Pediatrics

OFFICIAL PUBLICATION OF THE AMERICAN ACADEMY OF PEDIATRICS, INC.

VOL. 12 NOVEMBER 1953 No. 5

Editorial Board

HAROLD K. FABER, San Francisco
ALTON GOLDBLOOM, Montreal
PAUL A. HARPER, Baltimore
CHARLES A. JANEWAY, Boston
RUSTIN MCINTOSH, New York
CHARLES D. MAY, Iowa City
HERBERT C. MILLER, Kansas City, Kan.
RALPH V. PLATOU, New Orleans
MITCHELL I. RUBIN, Buffalo
FRANCIS F. SCHWENTKER, Baltimore
MILTON J. E. SENN, New Haven
JOSEPH STOKES, JR., Philadelphia

Contributing Editors

FEDERICO GÓMEZ, Mexico, D.F.
JOHN P. HUBBARD, Philadelphia
GROVER F. POWERS, New Haven
MYRON E. WEGMAN, New Orleans

HUGH MCCULLOCH, *Editor*
La Rabida Jackson Park Sanitarium, Chicago 49

Ex Officio

PHILIP S. BARBA, *President*, Philadelphia
EINOR H. CHRISTOPHERSON, *Executive Secretary*, Chicago

CONTENTS

ORIGINAL ARTICLES:

Recent Studies on Immunization Against Poliomyelitis—*Jonas E. Salk, M.D.* ... 471
Homozygous Type "c" Hemoglobin—*Theodore H. Spaet, M.D., Robert H. Alway, M.D., and Gaylord Ward, M.D.* ... 483
Persistence and Distribution of Toxocara Larvae in the Tissues of Children and Mice—*Margaret H. D. Smith, M.D., and Paul C. Beaver, Ph.D.* ... 491
Hemolytic Streptococcal Infection in Childhood—*Lowell A. Rantz, M.D., Margaret Maroney, M.D., and Joseph M. Di Caprio, M.D.* ... 498
Lymphoid Hyperplasia of the Appendix; Clinical Study—*Alfred A. Nathans, M.D., Hyman Merenstein, M.D., and Samuel S. Brown, M.D.* ... 516
Congenital Malformations and Birth Injuries in New York City—*Helen M. Wallace, M.D., Leona Baumgartner, M.D., and Herbert Rich* ... 525
Pseudocholedochal Cyst—*Arthur G. Smith, Captain, USAF (MC), and Sam F. Seeley, Brig. General, USAF (MC)* ... 536

(Continued on page iv)

CONTENTS

(Contents continued from page iii)

Hormone Patterns in Patients with Congenital Adrenal Hyperplasia—*Vincent C. Kelley, M.D., Ph.D., Robert S. Ely, M.D., and Richard B. Raile, M.D.* 541

Abnormal Electrolyte Composition of Sweat in Cystic Fibrosis of the Pancreas; Clinical Significance and Relationship to the Disease—*Paul A. di Sant'Agnese, M.D., Robert C. Darling, M.D., George A. Perera, M.D., and Ethel Shea, B.A.* 549

Clot Density Method of Fibrinogen Determination in Some Pediatric Conditions—*Abram Kanof, M.D., Samuel Losner, M.D., and Bruno W. Volk, M.D.* 564

Mucolytic Enzyme Systems. XX. Comparison of Mucoprotein and Hyaluronidase Inhibitor Concentrations in Maternal and Infant Serum—*Robert A. Good, M.D., Ph.D., Vincent C. Kelley, M.D., Ph.D., Thomas A. Good, M.D., and David Glick, Ph.D.* 575

SPECIAL SECTIONS:

Trends—*John P. Hubbard, M.D., Contributing Editor.* Secretary Hobby's Views on Federal Grants-in-aid 584

Public Health, Nursing and Medical Social Work—*Myron E. Wegman, M.D., Contributing Editor.* Juvenile Courts in the U.S.A.—*Will C. Turnbladh* 589

PEDIATRICS is owned and controlled by the American Academy of Pediatrics, Inc. Entered as second-class matter March 13, 1948, at the postoffice at Springfield, Illinois, and Menasha, Wisconsin, under the Act of March 3, 1879. Acceptance and a special rate of postage, as provided in Section 3440D, authorized November 18, 1952.

Copyright 1953, by the American Academy of Pediatrics, Inc. Printed in U.S.A.

Copyrighted in the British Commonwealth by Blackwell Scientific Publications, Oxford. No part may be duplicated or reproduced without permission of publishers.

TWENTY-THIRD ANNUAL MEETING

The American Academy of Pediatrics

October 3-7, 1954

Palmer House

Chicago

AREAL MEETING

April 5 to 7, 1954

Biltmore Hotel

Los Angeles

Pediatrics

VOLUME 12 NOVEMBER 1953 NUMBER 5

ORIGINAL ARTICLES

RECENT STUDIES ON IMMUNIZATION AGAINST POLIOMYELITIS

By JONAS E. SALK, M.D.
Pittsburgh

SOME six months ago we reported* the results of experiments in progress on immunization of human subjects against poliomyelitis. In that report it was shown that it was possible to induce the formation of poliomyelitis antibody using tissue culture fluids treated with formalin, emulsified with mineral oil, and administered intramuscularly. It was shown, also, that an aqueous preparation of the type 2 virus caused antibody to develop after intradermal inoculation. Although the results of studies available at the time of the first report provided the indications that we were seeking, they left much still to be done and many questions still to be answered.

I should like to take this opportunity to present preliminary results, from more recent experiments, that further substantiate the trends observed earlier. New observations have been made that leave no doubt that the poliomyelitis viruses abide by the well established laws of immunology and for this reason, if for no other, provide a basis upon which to anticipate the answers to certain questions that still remain to be resolved.

As has just been recalled, vaccines containing the mineral oil adjuvant were capable of inducing antibody formation to the three virus types, whereas antibody to the type 2 virus only could be evoked by aqueous preparations of the degree of potency then available. It was apparent even then that fluids of borderline potency, to be effective in stimulating antibody formation, required potentiation by means of the adjuvant, whereas a more potent preparation was demonstrably active, immunologically, without the adjuvant. This has been amply confirmed in the more recent studies, and the principal

From the Virus Research Laboratory, School of Medicine, University of Pittsburgh, Pittsburgh.

Read at the Twenty-Second Annual Meeting of the American Academy of Pediatrics, Miami, Oct. 9, 1953.

Aided by a grant from The National Foundation for Infantile Paralysis.

(Received for publication Oct. 10, 1953.)

* Salk, J. E., and others, Studies in human subjects on active immunization against poliomyelitis. I. Preliminary report of experiments in progress, J.A.M.A. **151**:1081, 1953.

purpose of this report is to present the evidence that it is possible to stimulate antibody formation to the three types of poliomyelitis virus, in human subjects, without as well as with the aid of the mineral oil adjuvant. This was made possible by the availability, for the studies here reported, of more potent fluids for conversion into vaccines.

Another question that could not be answered by the results of the earlier experiments was whether the prior immunologic experience of the subjects first available for study had any influence whatever upon the outcome of the findings that were made. It was shown that when antibody was present before vaccination, a further rise occurred, as if the inoculation had exerted a booster effect. It was shown, also, that if antibody was not present, a definite response also occurred. However, since there were not, in the first series reported in detail, any subjects who were free of antibody for all three types, it was not possible to say whether the previous contact with at least one of the immunologically distinct viruses may have altered their subsequent reactivity in such a way as to have been responsible in part for the effects observed. It has now been shown that children and adults, who have no antibody to any of the poliomyelitis viruses can form antibody to the three virus types.

There is a question in the minds of some as to whether persons in whom we find no evidence of serum antibody at the time of vaccination are really negative in this respect. The question has been asked as to whether some may not have levels of antibody too low to be measured by the tests in use. A further question has been advanced, as to whether persons who have no demonstrable antibody at the time of test may have had some at an earlier date and, therefore, cannot be considered strictly negative at the time of vaccination. These questions are of considerable theoretic importance, but from the practical viewpoint are of less significance, since antibody can be induced over a wide age span. The problem, if it be one at all, of distinguishing an immunologically experienced negative from an immunologically inexperienced negative, will be considered at a later time when studies in such persons are completed.

Another observation that is now well established is the extraordinary height to which antibody level can be raised in persons who have some antibody at the time of vaccination. Although our data are meager for persons in whom the initial antibody response was induced artificially, there is ample substantiation of the occurrence of this effect in persons whose antibody was formed as a result of a previous natural exposure.

The question has also been raised as to whether the virus preparations employed in our studies were completely devoid of living virus. It is possible to say without equivocation that the effects observed in our initial studies, as well as those to be reported here, are due to the antigenic substance in the inoculum, and not due to multiplication of particles of infectious virus that may be postulated to be present. This statement is made not only because all laboratory tests indicate complete inactivity and because an additional measure of treatment was added to increase the margin of safety to a point beyond which all doubt would disappear, but for reasons based upon the character of the immunologic response. The evidence for the latter is as follows: In both man and experimental animals possessing some antibody, the injection of even a small amount of vaccine evokes a marked response. A response of this degree would not be expected if the effect was due to living virus since the circulating antibody would, very probably, neutralize the injected virus promptly, especially when the inoculum is administered intramuscularly. In further support of the belief that no infectious virus is present is the observa-

tion that in some persons with no antibody before vaccination, the response is low, or fails to occur, until a second dose is given; unlike that which would have been expected if the effect was due, either entirely or in part, to multiplication of living virus.

The longest postvaccination interval observed in the present series is 3 to 4 months; the longest interval in the initial series is now one year. Although the one-year serum samples have not yet been tested, some drawn at seven months after two doses of an aqueous type 2 vaccine have been examined and revealed either little or no decline in titer from that observed earlier. Even though the trend suggests a moderate degree of persistence of antibody, conclusions should not yet be drawn, nevertheless, until longer intervals have elapsed and a sufficient number of sera from more subjects have been tested.

It is desired to comment that in addition to improvements in the viral content of fluids available for conversion into experimental vaccines, and to improvements in the safety tests, considerable progress has been made in improving the method for destroying infectivity by treatment with formaldehyde. Unfortunately, these procedures had not yet been adequately developed for the preparation of the vaccines employed in the studies to be reported here; the procedures now in use require much smaller quantities of formalin than had been used heretofore, with much more effective retention of antigenicity. It is reasonable to state, therefore, that the results to be described represent the findings obtained with materials that, in terms of methods now available, are obsolete and therefore do not reveal the full potentiality of the application of the principles upon which the present approach is based.

Plans for testing such material had to be interrupted because of the occurrence of a case of poliomyelitis in the community in which these studies were to be carried out. It seemed wise to postpone further studies to avoid the possible coincidental inoculation of vaccine into a child who might be well along in the incubation period and, therefore, possibly confuse the question of clinical safety of a preparation that, from the labora-

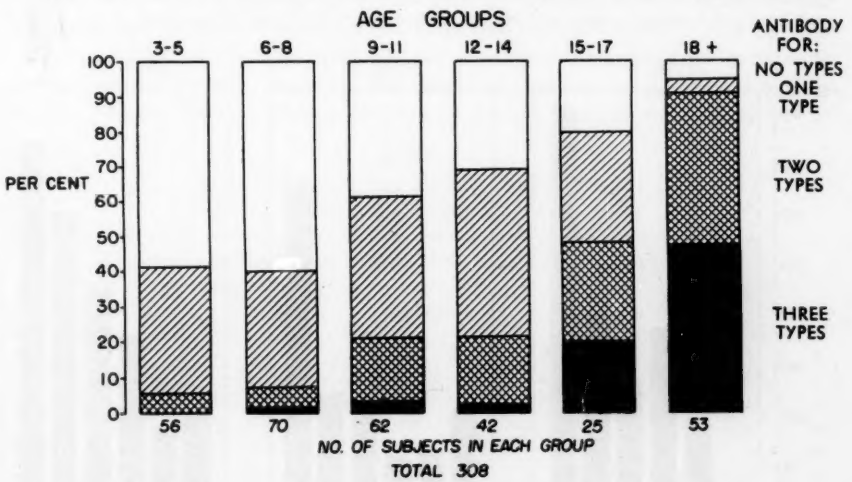


CHART 1. Antibody for one or more types of poliomyelitis virus in different age groups.

tory viewpoint, appears safe. It will be necessary, therefore, to resume this work after the current poliomyelitis season; and many of the questions still unanswered will then be investigated.

Subjects

The persons who participated in the studies begun in the late spring of 1953 were for the most part residents of Allegheny County and the majority were from the vicinity of Sewickley and Leetsdale, Pa.; these are communities nearest The D. T. Watson Home in Leetsdale where the work was done. At first, both children and adults were included, but subsequent tests were limited to children in the age group 4 to 12. Of the group of 474 in these studies, some were given aqueous vaccine only, some received only the adjuvant vaccine, and others a combination of the 2 on different occasions.

The age distribution of part of the group now under study is shown in chart 1. It may be seen from this figure that approximately 60% of children between the ages of 3 and 8 yr. possessed no antibody for any of the 3 virus types. An additional number, amounting to more than 30%, had antibody for one type; and a proportion considerably less than 10% had antibody for 2 types; only an occasional child of this age had antibody for 3 types. With increasing age a higher proportion of subjects were found to have antibody for one or more types but many are still susceptible as suggested by the absence of antibody for one or more of the poliomyelitis viruses. In this particular sampling there were 53 persons 18 yr. of age or over, and less than 50% of them had antibody for all 3 types. Considering the frequency of occurrence of antibody for types 1, 2 and 3 separately in each of the age groups, the data in chart 2 are shown; here again one can see the relatively high proportion, especially in the lower age group, who have no antibody for the different viruses.

Materials and Procedures

The vaccines employed are to be described in more detail elsewhere. They had been prepared when we were still destroying infectious activity with 1:250 formalin at the temperature of melting ice rather than the more efficient method using less formalin at 35°C.; nor were the fluids that were made into vaccine as potent, in respect to viral content, as the material we now possess. Nevertheless, it is of interest to examine the trends, evident from the serologic data thus far available.

The determination of serum antibody titers is time-consuming and it will be some months before tests are completed on the many postvaccination serum samples that have to be compared with specimens drawn before vaccination. The problem is further complicated by the fact that each serum must be tested 3 times, to determine titer of antibody for each of the 3 virus types. It was for this

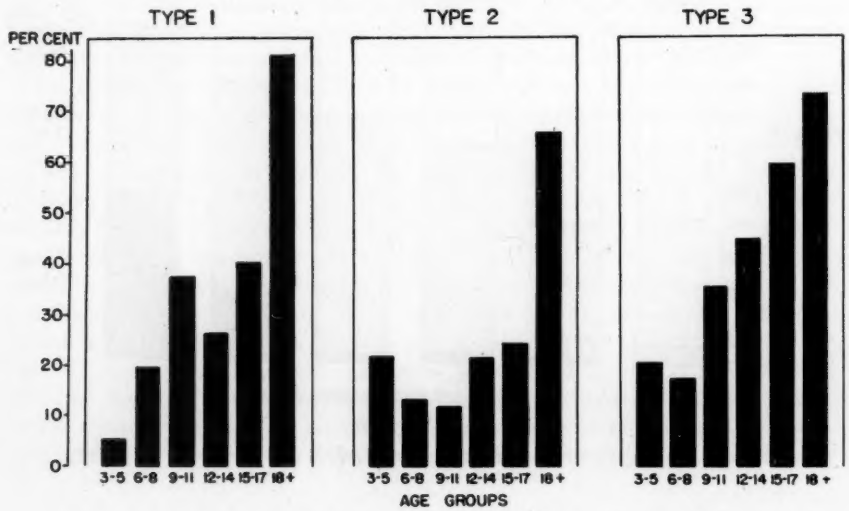


Chart 2. Percentage of each age group with antibody for 3 types of poliomyelitis virus.

TABLE 1

THREE DOSES OF AQUEOUS VACCINE GIVEN INTRAMUSCULARLY AT INTERVALS OF ONE WEEK

Responses at 3 to 6 wk. in Subjects with Prevaccination Antibody For																		
No Types							One Type							Two Types				
Age yr.	Prevacc. 1	2	3	Postvacc. 1	2	3	Age yr.	Prevacc. 1	2	3	Postvacc. 1	2	3	Age yr.	Prevacc. 1	2	3	Postvacc. 1	2	3
6	0	0	0	+	+	+	4	+	0	0	+	+	+	A	+	+	0	+	+	+
7	0	0	0	+	+	+	6	+	0	0	+	+	+	14	+	0	+	+	+	+
8	0	0	0	+	+	+	8	+	0	0	+	+	+	15	+	0	+	+	+	+
9	0	0	0	+	+	+	13	+	0	0	+	+	+	A	+	0	+	+	+	+
9	0	0	0	+	+	+	3	0	+	0	+	+	+	A	+	0	+	+	+	+
10	0	0	0	+	+	+	4	0	+	0	+	+	+	A	0	+	+	+	+	+
10	0	0	0	+	+	+	5	0	+	0	+	+	+	A	0	+	+	+	+	+
11	0	0	0	+	+	+	5	0	0	+	+	+	+							
12	0	0	0	+	+	+	7	0	0	+	+	+	+							
							12	0	0	+	+	+	+							

0 = Antibody level of <4 1, 2, 3 = Types 1, 2, 3
+ = Antibody level of 1:4 or greater
A = Adult

reason that a rapid answer was sought through a screening test of all serum samples, at a dilution of 1:4, using approximately 32 50% tissue-culture infecting doses of virus. Two cultures of monkey kidney tissue were used for the screening test but 3 cultures for each 4-fold serum dilution was used in the quantitative titrations.

RESULTS

The results of the screening tests in persons from four groups vaccinated in different ways are illustrated in the accompanying tables. Table 1 shows the results of tests for antibody for each type before, and at 3 or 6 weeks after the start of vaccination in a group of 26 individuals given three 1.0 cc. doses of aqueous vaccine, inoculated intramuscularly, and at intervals of one week. Each dose contained 0.33 cc. fluid for each type. It is readily evident from this table that a uniform conversion from negative to positive occurred whenever there was no detectable antibody before vaccination. This was true both for the nine persons who had no demonstrable antibody for any type as

TABLE 2

TWO DOSES OF AQUEOUS VACCINE + ONE DOSE OF ADJUVANT VACCINE GIVEN INTRAMUSCULARLY AT INTERVALS OF ONE WEEK

Responses at 3 to 6 wk. in Subjects with Prevaccination Antibody For																		
No Types							One Type							Two Types				
Age yr.	Prevacc. 1	2	3	Postvacc. 1	2	3	Age yr.	Prevacc. 1	2	3	Postvacc. 1	2	3	Age yr.	Prevacc. 1	2	3	Postvacc. 1	2	3
9	0	0	0	+	+	+	12	+	0	0	+	+	+	9	+	+	0	+	+	+
9	0	0	0	+	+	+	14	+	0	0	+	+	+	A	+	+	0	+	+	+
12	0	0	0	+	+	+								A	+	+	0	+	+	+
12	0	0	0	+	+	+								A	+	0	+	+	+	+
13	0	0	0	+	+	+								A	+	0	+	+	+	+
16	0	0	0	+	+	+								A	0	+	+	+	+	+
16	0	0	0	+	+	+														

TABLE 3

THREE DOSES OF AQUEOUS VACCINE GIVEN INTRADERMALLY AT INTERVALS OF ONE WEEK

Responses at 3 to 6 wk. in Subjects with Prevaccination Antibody For

No Types							One Type							Two Types						
Age	Prevacc.			Postvacc.			Age	Prevacc.			Postvacc.			Age	Prevacc.			Postvacc.		
yr.	1	2	3	1	2	3	yr.	1	2	3	1	2	3	yr.	1	2	3	1	2	3
7	0	0	0	+	+	+	12	+	0	0	+	+	+	11	+	+	0	+	+	+
12	0	0	0	+	+	+	15	+	0	0	+	+	+	A	+	+	0	+	+	+
12	0	0	0	+	+	+	16	+	0	0	+	0	0	10	+	0	+	+	+	+
20	0	0	0	+	+	+	17	0	+	0	+	+	+	10	+	0	+	+	+	+
5	0	0	0	+	0	+	5	0	0	+	+	+	+	A	+	0	+	+	+	+
15	0	0	0	+	0	+	5	0	0	+	+	+	+	4	0	+	+	+	+	+
							6	0	0	+	+	+	+	13	0	+	+	+	+	+
							7	0	0	+	+	+	+	15	0	+	+	+	+	+
							9	0	0	+	+	+	+	A	0	+	+	+	+	+
							9	0	0	+	+	0	+							

well as in the remainder who, before vaccination, had antibody for one or two types. The actual titer of antibody in persons from this group will be presented in later tables.

Table 2 contains similar data for 15 individuals in the group given two doses of aqueous vaccine followed by one dose of adjuvant vaccine on the same time schedule as in the previous group. The adjuvant vaccine consisted of 0.6 cc. emulsion containing 0.1 cc. fluid for each type. Table 3 contains similar data for a group of 25 individuals given three doses intradermally, a week apart. On each occasion three sites were injected with 0.1 cc. of the respective types. Table 4 contains data for a group of 17 persons given virus adsorbed on calcium phosphate, followed in two weeks by an injection of aqueous vaccine. The two different inocula were used because the adsorbed viral vaccine was inadvertently left in the laboratory and the aqueous vaccine was therefore substituted at the last minute.

TABLE 4

ONE DOSE VIRUS ADSORBED ON CALCIUM PHOSPHATE + ONE DOSE AQUEOUS VACCINE, BOTH GIVEN INTRAMUSCULARLY AT INTERVALS OF TWO WEEKS

Responses at 3 to 6 wk. in Subjects with Prevaccination Antibody For

No Types							One Type							Two Types						
Age	Prevacc.			Postvacc.			Age	Prevacc.			Postvacc.			Age	Prevacc.			Postvacc.		
yr.	1	2	3	1	2	3	yr.	1	2	3	1	2	3	yr.	1	2	3	1	2	3
3	0	0	0	+	+	+	12	+	0	0	+	+	+	5	+	+	0	+	+	+
							A	+	0	0	+	+	+	7	+	+	0	+	+	+
							A	+	0	0	+	+	+	16	+	+	0	+	+	+
							7	0	+	0	+	+	+	A	+	+	0	+	+	+
							13	0	0	+	+	+	+	9	+	0	+	+	+	+
							A	0	0	+	0	+	+	10	+	0	+	+	+	+
														13	+	0	+	+	+	+
														18	+	0	+	+	+	+
														A	+	0	+	+	+	+
														4	0	+	+	+	+	+

It is clear from the data in the foregoing tables that vaccines without mineral oil are capable of creating antibody where it did not exist before and in amounts that are measurable. Now it will be necessary to determine whether the effect induced with the aqueous vaccine is adequate. If the adjuvant is not required for inducing antibody formation, it remains to be seen if it can be used advantageously to increase antibody titers to higher levels, or to reduce the number of inoculations, or to prolong the effect. We shall not try to answer the latter questions at this time, but will consider merely the evidence available concerning the levels of antibody induced in the first three of the groups for which screening information has been presented.

Table 5 contains a summary of the results of antibody titrations before and 3 to 6 weeks after vaccination in some of the individuals referred to in table 1. It is evident

TABLE 5

THREE DOSES OF AQUEOUS VACCINE GIVEN INTRAMUSCULARLY AT INTERVALS OF ONE WEEK

Subject	Age	Titer of Antibody Before and 3 to 6 wk. After Start of Vaccination					
		Type 1		Type 2		Type 3	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
F-43	13	22	>1024	0	32	0	8
F-44	6	512	>1024	0	32	0	32
F-337	8	512	>1024	0	64	0	32
F-52	7	0	32	0	64	90	>1024
F-53	12	0	32	0	32	128	>1024
F-54	5	0	22	0	44	90	>1024
F-13	12	0	22	0	11	0	22
F-101	8	0	45	0	22	0	8
F-332	7	0	11	0	101	0	8

from this table that the most dramatic responses were observed in persons who, at the time of injection, possess some antibody as a residual from an earlier natural exposure. The indications are that antibody levels induced by the natural disease tend to decline gradually; the more recent the infection, the higher the titer. When the titer of naturally acquired antibody has declined to what seems to be a stabile level, then it appears that a small dose of antigen provides a tremendous "booster effect." Persons who have no detectable antibody for a given type, but who have antibody for one or both of the two remaining types, seem to respond slightly better than do persons who have no detectable antibody for any of the three types. However, this response is not at all comparable to that observed for the types for which some naturally acquired antibody is present. This is an interesting phenomenon and is under more careful study; from the practical viewpoint, it matters little since persons with antibody for one or two types can become severely paralyzed in the course of infection with viruses for which they are deficient in antibody—for this there is ample evidence.

It is evident that the levels of antibody induced are quantitatively much lower if no antibody is present before vaccination than if naturally acquired antibody is present, as to suggest a qualitative difference in the mechanism of the response to primary or secondary stimulation. It is clear that the well known "booster phenomenon" is operative;

TABLE 6

THREE DOSES OF AQUEOUS VACCINE GIVEN INTRADERMALLY AT INTERVALS OF ONE WEEK

Subject No.	Age	Titer of Antibody Before and 3 to 6 wk. After Vaccination					
		Type 1		Type 2		Type 3	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
F-103	15	0	350	45	2850	128	1430
F-304	A	0	90	32	1430	32	512
F-72	4	0	32	32	1024	128	1430
F-104	13	0	32	0	512	8	1430
F-74	15	712	5730	0	128	0	12
F-85	12	32	5730	0	128	0	8
F-84	17	0	90	32	712	0	0
F-82	10	0	8	0	8	45	2048
F-59	9	0	0	0	8	32	700
F-81	7	0	32	0	45	178	1430
F-56	5	0	8	0	8	32	512
F-93	6	0	12	0	4	128	512
F-94	5	0	22	0	8	128	512
F-76	9	0	8	0	0	90	350
F-90	20	0	22	0	4	0	22
F-77	7	0	6	0	8	0	8
F-50	5	0	8	0	0	0	4
F-75	15	0	4	0	0	0	4

TABLE 7

TWO DOSES OF AQUEOUS VACCINE PLUS ONE DOSE OF ADJUVANT VACCINE GIVEN INTRAMUSCULARLY AT INTERVALS OF ONE WEEK

Subject	Age	Titer of Antibody Before and 3 to 6 wk. After Start of Vaccination					
		Type 1		Type 2		Type 3	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
F-58	A	45	2048	128	512	0	+
F-61	9	512	>4096	8	512	0	+
F-65	12	+	+	16	64	0	+
F-67	A	+	+	64	2048	0	+
F-70	A	+	+	0	64	+	+
F-68	A	+	+	0	48	+	+
F-38	A	0	45	32	2048	0	+
F-66	14	+	+	0	64	0	±
F-41	9	0	32	0	16	0	+
F-42	13	0	32	0	8	0	+
F-49	12	0	32	0	8	0	+
F-51	9	0	45	0	12	0	+
F-69	16	0	+	0	4	0	+
F-71	12	0	+	0	8	0	+

but we have made very limited beginnings in applying this in the human studies. This is one of the first problems to be explored when the vaccination of children is next resumed, and this will be done particularly in children who have no demonstrable antibody for any of the three types.

Tables 6 and 7 show the same kinds of data for persons in two of the other vaccinated groups referred to in tables 3 and 2, respectively. It will be seen in table 6 that three doses intradermally may be slightly less effective than a similar schedule involving larger volumes intramuscularly (table 5). The relative value of these two routes of inoculation are to be studied further. In table 7 are data for individuals in the group given two aqueous doses followed by one adjuvant dose, each given a week apart. Although it may

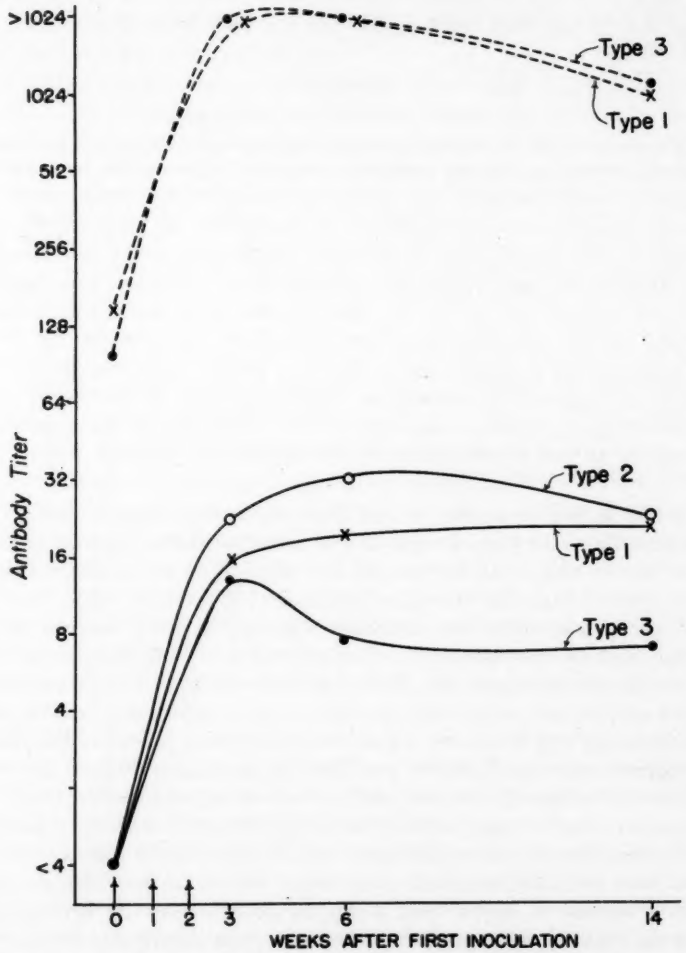


CHART 3. Mean antibody titer at intervals after 3 doses of aqueous vaccine given intramuscularly at intervals of 1 wk.

not be possible to see the advantage of this over the course involving three aqueous doses, it can be said, from the small amount of information available, that the consistency of effect, the height of antibody titer, and its persistence over a 3 to 4 month period appear to be better in the group given the adjuvant vaccine for the third dose. That this advantage would be present is not surprising, but whether it is necessary is a matter still to be determined. It is clear, however, that a means is available for manipulating the antigenic effect in this way.

The curves in chart 3 are presented to illustrate the trends indicating the level and degree of antibody persistence observed in a group of nine subjects given three doses of aqueous vaccine intramuscularly. The relationships observed make one wonder whether a booster dose at 3 to 6 weeks, or beyond, in persons whose antibody was induced by vaccine, will cause a reaction similar to that seen in persons whose antibody resulted from a natural exposure.

TABLE 8

INFLUENCE OF TWO DOSES SIX WEEKS APART

(First was weak preparation with adjuvant, second was aqueous vaccine without adjuvant that did not elicit antibody formation on first dose in subjects with no antibody to any type before vaccination.)

	F-197 Age 9				F-338 Age 3				F-193 Age 6				F-195 Adult			
Type 1	0	0	0	101	0	0	0	8	0	8	8	32	45	712	2048	6000
Type 2	0	0	0	16	0	0	0	256	0	0	0	32	0	8	8	64
Type 3	0	0	0	+	0	0	0	+	0	0	0	+	0	0	0	+
	↑		↑		↑		↑		↑		↑		↑		↑	
	0	3	6	12	0	3	6	12	0	3	6	12	0	3	6	12
	wk.				wk.				wk.				wk.			

Antibody titer for types indicated at intervals after first dose.
↑ indicates when injections were given.

The answer to this can be had, in part, from information available thus far in only four subjects. They were given a single dose of one of the earliest adjuvant vaccines, and it will be seen in table 8 that the younger ones who had no pre-antibody to any of the three types, by and large, did not respond measurably; however, one adult, who had antibody for type 1 virus, exhibited a remarkable response even to the small dose of antigen in the first injection. Subsequently, a second injection was given, using an aqueous vaccine, and in all instances appreciable levels of antibody developed for all three virus types. The serum samples have been titrated for types 1 and 2 antibody only, and the screening test performed for type 3 indicates a positive reaction which previously had been negative. It might be questioned whether the delayed appearance of antibody may not have been due to the fact that the first injection was with an adjuvant vaccine; however, from other experiences this is highly unlikely, and the appearance of antibody, although tested about six weeks after the second injection, appears to be directly related to the second injection. Since one injection of this same vaccine did not, in other subjects, induce as consistent a response as shown here, it may be concluded that the first injection, although it did not bring about an effect that was measurable directly may nevertheless have been effective in priming the immunologic mechanism to respond more efficiently when a second injection was given.

Discussion

It is clear from the data presented in this report that studies already begun will have to be continued for further elucidation of many details. But, the question can justifiably be asked, "Why can't we try these methods of conferring antibody actively, by the use of an experimental vaccine, even in the present imperfect stage of development, to see if paralysis can be prevented?" The reply would be that if, with material that has been produced and processed on a large scale basis, antibody can be induced consistently and in as close to 100% of persons as possible, and if this effect can be expected to persist over a period of one season, at least, then there are no good reasons for not doing so, as long as the public at large, as well as our colleagues, understand that this is precisely what we are doing. We do not want to allow any distortion of the fact that we are still actively in the stage of clinical investigation; and that this work must be continued, but it must be continued gradually and cautiously.

If and when a study is made to determine the effectiveness of any vaccination procedure, there are several approaches from which to choose. One is that of a controlled study involving the injection of alternate children with either vaccine or a control preparation consisting of either another biologic preparation such as a vaccine for another disease, or of physiologic salt solution. This method has the incomparable advantage that it is "strictly scientific" in the orthodox sense and would allow a comparison of two strictly comparable groups without any possibility of bias in diagnosis in the follow-up period. Such a study could be conducted with the participation of children of elementary school age in widely scattered communities.

Another type of controlled study might involve the use of the poliomyelitis vaccine under test in children of a narrowly restricted age group, preferably the one of highest incidence, and that in this way information be accumulated relative to efficacy in preventing the paralytic disease; this would be done through an analysis of age specific attack rates within each vaccinated community, as well as comparisons between vaccinated and unvaccinated siblings. For simplicity of administration and greatest efficiency in deriving the most information, such observations could best be made in children in the first grade in schools in many parts of the country. In a study of this type the controls would consist of: (1) younger and older siblings of the vaccinated children; (2) younger and older children in the same school or community; (3) children of the same age in other communities; (4) past experience in children of the vaccinated age group in the community selected for study. If no protective effect is observed the testing of vaccination in this way can be stopped, or it can be continued with modifications until success is achieved.

Through either approach an answer is assured but "when" can not be predicted. Questions that may be raised concerning the persistence of effect beyond one season, and the need for booster doses at long intervals must remain as secondary until the primary questions have been answered concerning the protective value for one season.

For reasons so well presented by Dr. Johannes Ipsen* in the September 1953 issue of the *American Journal of Public Health,* it is necessary to give due attention to information that is given to the public that provides them with the basis for the attitude that will prevail. If a well controlled plan is to be evolved we must emphasize that a vaccine for

* Ipsen, J., Jr., Administrative problems in use of poliomyelitis immune globulin, Am. J. Pub. Health 43:1101, 1953.

general use is not yet here. In the studies reported here, with experimentally prepared vaccines, we have merely shown that, in terms of inducing some antibody formation, there now is a choice as to the use of aqueous or emulsified vaccines. This step forward is related to success in improving the viral content of fluids used for preparing a vaccine, and to the use of multiple inoculations; that this might be possible, was suggested from our earlier report. We have still to show, in human subjects, the benefits that can accrue from better methods of formalin inactivation and the full advantage of the adjuvant when allowed to react with an adequate antigenic mass properly treated for destruction of viral activity. Nor have we as yet had the opportunity to demonstrate the optimal application of the booster effect with aqueous preparations by proper spacing of inoculations.

Problems relative to mass production are being resolved rapidly in several laboratories, and the clear indications at present are that this may be one of the simplest biologic preparations to make. The fact that, at the moment, monkey-kidney tissue is required is not a problem, as is imagined by many, because relatively large amounts of potential vaccine can be derived from the tissue of a single animal.

Conclusion

The simple fact is: That an experimental method for inducing measurable amounts of antibody for the three known poliomyelitis viruses, employing a killed-virus vaccine is available, and it now becomes possible to determine whether—and to what extent—the incidence of naturally occurring paralysis may be influenced.

All that should be inferred now is that studies are progressing satisfactorily; there have been no set-backs nor anything but revelations that shed more light on the course ahead. We must continue to regard the experimental developments to date as providing immunologic markers along the way that tell us whether we are on the right road. That there is more to do now than before indicates that we have not stumbled down a by-way but have selected a road, with many lanes, that seems long indeed. Our problem is to select not only the fast lane but the one that is safest and most certain.

University of Pittsburgh School of Medicine

HOMOZYGOUS TYPE "c" HEMOGLOBIN

By THEODORE H. SPAET, M.D., ROBERT H. ALWAY, M.D., AND GAYLORD WARD, M.D.
San Francisco

PAULING and associates[1] reported in 1949 that the hemoglobin of patients with sickle cell disease had an abnormal electrophoretic mobility. Since that time two additional abnormal hemoglobins have been identified by electrophoretic methods. One of these hemoglobins migrates in the electrophoretic field as a more positively charged particle than either the normal or the sickle pigments, and has been termed "type III".[2] The other has a mobility identical to that of sickle hemoglobin, being intermediate between the normal and type III varieties; but it differs from sickle hemoglobin by its greater solubility in the reduced state, and in its inability to impart sickling to erythrocytes.[3] Itano[3] has proposed that normal, sickle, type III, and the last-mentioned hemoglobin be designated "a," "b," "c," and "d," respectively. This terminology simplifies nomenclature in a field of rapidly growing complexity, and will accordingly be used in the present report.

TABLE 1

EFFECTS OF VARIOUS KNOWN COMBINATIONS OF ABNORMAL HEMOGLOBINS

Common Nomenclature	Hemoglobin Combination*	Anemia	Erythrocyte Morphology
Sickle cell trait	ab	Absent	Normal; sickling only in reducing medium
Sickle cell anemia	bb	Severe	Target cells; sickle cells even on direct smear
III trait	ac	Absent	Target cells
III plus sickle	bc	Mild	Target cells; sickling only in reducing medium
None	ad	Absent	Not reported
None	bd	Present	Not reported. Sickling in reducing medium

* For explanation of nomenclature, see text.

To the time of the present writing neither the "c" nor the "d" hemoglobins have been reported in pure form in the erythrocytes of patients. They have been found only in combination with the "a" or "b" pigments. Table 1 shows the clinical and hematologic features associated with the various hemoglobin patterns that have been encountered. The patient to be reported had hemoglobin which migrated electrophoretically as pure type "c."

REPORT OF CASE

B.F., Negro boy 4 yr. of age, had been in good health until 3 wk. prior to his admission. The course leading to hospitalization started with right periorbital swelling followed shortly by similar involvement on the left. No pain, fever, or other systemic manifestations had been noted. No trauma was reported, nor was the past history contributory.

From the Departments of Medicine and Pediatrics, Stanford University School of Medicine, and the San Francisco County Hospital, San Francisco.

(Received for publication March 6, 1953.)

No suggestion of hemolytic disease was elicited from the family history. Both parents and 2 siblings were reported living and well; however, the mother and siblings were not available for study.

On physical examination the patient was not obviously ill. He appeared to be of the stated age; and his height, weight, general development, pulse, temperature, blood pressure, and respirations were normal. A diffuse, semifluctuant and slightly tender swelling covered the left temporal area, but periorbital edema was not found. Several small, soft nontender lymph nodes were palpated in the anterior cervical, axillary, and inguinal regions. The tip of the spleen was felt just below the costal margin. No other abnormalities were noted.

Hematologic data are presented in table 2. Essentially they showed a leukocytosis which was initially neutrophilic, but subsequently became lymphocytic; and a transient and mild anemia in which the outstanding feature was the presence of numerous target cells. A minimal reticulocytosis was found in occasional blood counts, and small numbers of normoblasts were consistently seen in

TABLE 2

HEMATOLOGIC DATA OF PATIENT B.F.

(Range during period of study)

Hgb.	9.8–14.0 gm./100 cc.
RBC count	3.25–5.00 million/mm.^{3}
Hematocrit	30–39%
WBC count	14.2–27.0 thousand/mm.^{3} (30–62% lymphocytes)
Reticulocytes	0.8–1.2%
Platelets	180,000–200,000/mm.^{3}
Blood type	$0\ \frac{cDe}{c?e}$

Bone marrow differential count:

	%
Myeloblasts	0.0
Promyelocytes	0.2
Myelocytes	7.4
Metamyelocytes	8.0
Band forms	9.0
Segmented forms	7.2
Eosinophils	2.2
Basophils	0.2
Plasma cells	0.4
Lymphocytes	20.4
Monocytes	1.4
Normoblasts	41.6

the peripheral blood smear. Bone marrow showed a moderate erythroid hyperplasia. Red blood cells were normochromic and normocytic, and no sickling was demonstrable by the sodium bisulphite method. Negative results were obtained in the following laboratory studies: urinalysis, tuberculin test, serologic tests for syphilis, cephalin flocculation, van den Bergh, heterophile agglutination, bleeding time, clotting time, clot retraction. Serum proteins were 5.9 gm./100 cc with 3.5 gm. albumin and 2.4 gm. globulin. Icteric index was 6.7.

The temporal swelling was incised and about 10 cc. of blood were expressed with pressure. No purulent material was obtained. The swelling did not recur and the incision healed without incident. The remainder of the hospital course was asymptomatic. Two weeks after admission a 200 cc. venesection was performed in order to obtain blood for erythrocyte survival studies. This was well tolerated, and rapid restoration of the blood count to previous levels occurred. The patient was discharged 2 mo. after admission; he was evidently well except for a persistent lymphocytosis.

Special Studies

The presence in the peripheral blood of numerous target cells and persistent normoblasts led to the performance of further studies designed to elucidate the possibility of a latent hemolytic process. These studies were as follows:

Electrophoretic Identification of Hemoglobin: The patient's hemoglobin was subjected to paper electrophoresis according to technics previously described.[4] Consistently a single band was obtained corresponding to the location of type "c." No pigment was seen at the normal position. This pattern is shown in figure 1. Electrophoretic analysis of these hemoglobins was also performed in the Tiselius Apparatus by Dr. H. A. Itano at the California Institute of Technology in Pasadena, and identical results were obtained.

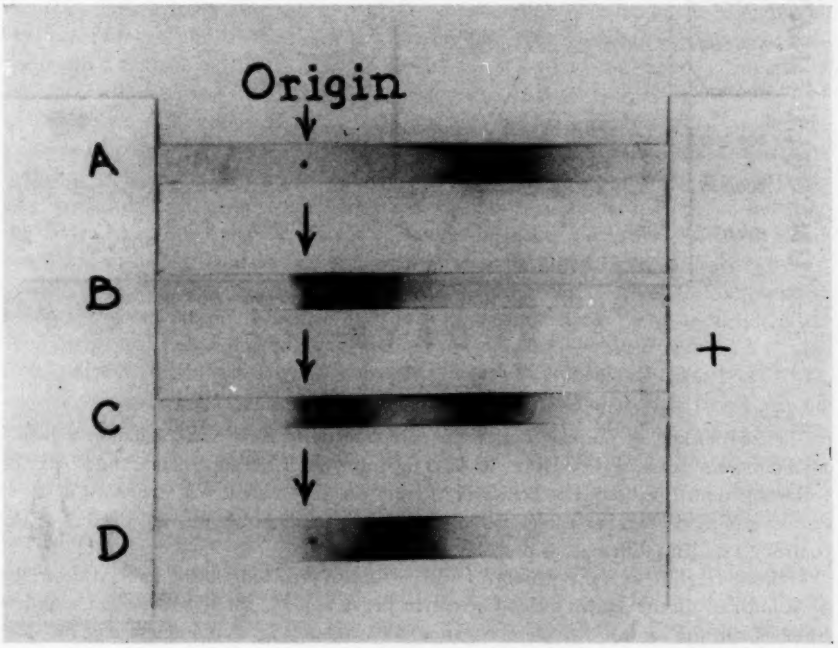


Fig. 1. Paper electrophoretic patterns of hemoglobins. A. Normal control. B. Patient B.F. C. Father of Patient B.F. D. Sickle cell anemia control.

Fetal hemoglobin was measured by the method of Singer et al.[5] No fetal hemoglobin was found in the patient's blood.

Fecal urobilinogen output was measured on a four day total stool collection in which timing was controlled by means of carmine markers. The technic of Watson[6] was used to determine the pigment. The output of fecal urobilinogen was 135 mg./day, a figure about twice normal for a child of this age.[7]

Mechanical fragility of the erythrocytes was studied in the following manner: The patient's erythrocytes were washed three times in isotonic saline. One cc. of washed, packed cells was suspended in 4 cc. of isotonic saline. The cell suspension was placed in a glass test tube containing ten 3 mm. glass beads, and was agitated for two hours in a

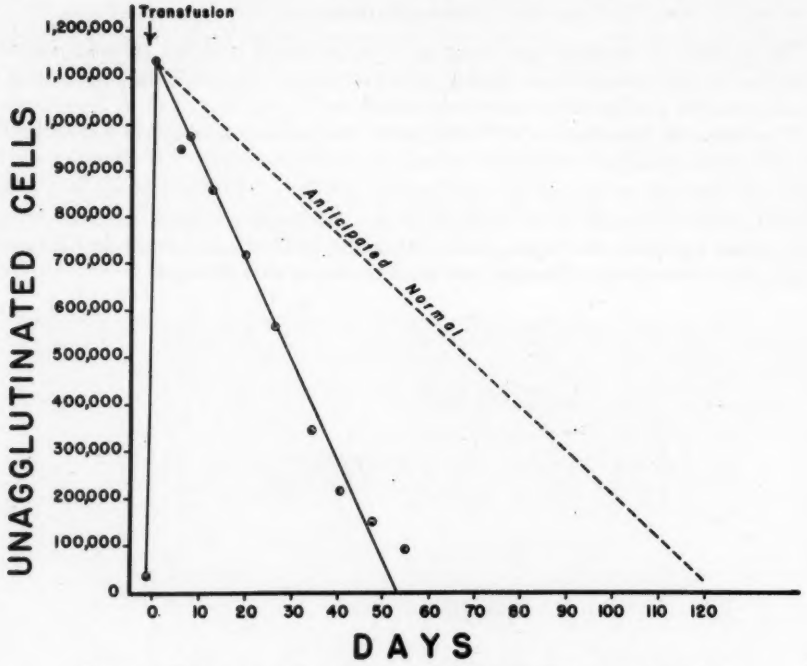


CHART 1. Disappearance of patient's erythrocytes (type O) in normal recipient (type A), as measured by Ashby technic.

mechanical shaker. A normal control was simultaneously run. After agitation a hemoglobin determination was taken of the total mixture and of the supernatant fluid obtained following centrifugation. The hemoglobin from the supernatant was expressed as a per cent of the total. The percentage hemolysis of the patient's cells was 2.8%; that of the control 2.1%. This difference is probably insignificant.

Osmotic fragility of the erythrocytes was performed according to the method described by Wintrobe.[8] In the patient's blood hemolysis began at .45% saline but was not complete by .21%. In the control, hemolysis began at .54% saline and was complete at .32%. It is evident that the cells of the patient showed a significant increase in resistance to hypotonic hemolysis, a phenomenon commonly associated with the presence of target cells.

The survival time of the patient's erythrocytes was determined by a modification of the Ashby technic.[9] The patient was type O, Rh-positive. Two hundred cc. of his blood was transfused into a child who was hematologically normal but was suffering from a meningocele. The recipient was type A, Rh-positive. Chart 1 shows the unagglutinable cell count on the normal recipient following transfusion of the patient's blood. It shows the survival time of the patient's cells to be about 55 days. The disappearance of the transfused cells proceeded in a linear manner, indicating that the patient's erythrocytes were uniformly abnormal, all having about the same shortened life span.

Family Studies: Unfortunately the father was the only other member of the family available for study. He was free of clinical signs and symptoms and was not anemic. However, moderate numbers of target cells were found in his peripheral blood, and his

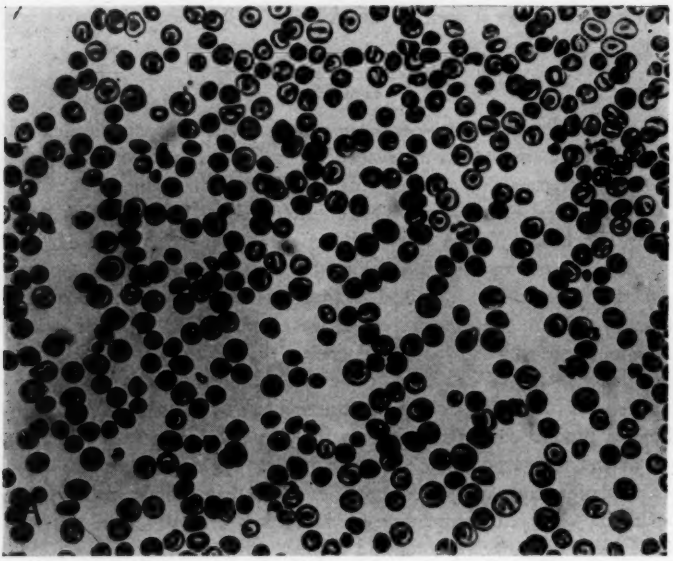
hemoglobin showed bands at both the normal and "c" positions on electrophoretic analysis (see Fig. 1).

Discussion

The patient described in the present report was presented for medical care not because of hemolytic anemia, but rather because of an unrelated hematoma of the scalp. The origin of this latter condition was unexplained. The striking appearance of the erythrocytes in the peripheral blood smear directed attention to the possibility of an abnormal hemoglobin. The blood picture was characterized by an extremely high percentage of target cells, the absence of hypochromia, and occasional normoblasts. Homozygous type "c" hemoglobin was readily identified by paper electrophoresis. Although anemia was only transiently present, a hemolytic process was demonstrated by the increased output of fecal urobilinogen, and by the shortened survival time of the patient's erythrocytes transfused into a normal individual. Despite the hemolytic process, the patient is apparently able to compensate for a red blood cell destruction rate of about twice normal by doubling his erythrocyte production. In response to the demand for increased blood production occasioned by the venesection, the bone marrow even further augmented its output. This finding is in conformity with previous studies which have shown that the bone marrow has a remarkable ability to compensate for blood loss or destruction. Provided sufficient iron is available, there may be a tenfold increase in blood production following blood loss;[10] and in hemolytic anemias a sevenfold increase in output can be attained.[11]

Although the patient has manifested no apparent ill effects from his compensated hemolytic process, potentially certain disorders may be anticipated. For example, increased blood destruction proceeding over long periods of time may lead to the formation of pigment stones in the biliary system. Also mild "crises" may occur in which anemia will become manifest. Singer[12] states that transient periods of bone marrow inactivity may be found in normal individuals. If this view is correct, patients suffering from hemolytic disease will be more susceptible to anemia during such episodes owing to the decreased longevity of their erythrocytes. It is realized that these prognostications are purely hypothetic in this case. The child had been singularly free of symptoms to the time of his hospital admission.

The differential diagnosis of type "c" hemoglobin is essentially that of distinguishing between those disorders in which target cells are found in large numbers. Crosby[13] has classified the conditions associated with target cells into five main groups: 1. the osmotic target cell, associated with dehydration; 2. the postsplenectomy target cell; 3. the target cell of liver disease; 4. the target cell of sickle cell anemia; 5. the target cell of hypochromia, mainly seen in thalassemia. Of these conditions, only thalassemia minor offers a diagnostic problem, as the others show characteristic clinical pictures or can be readily identified by simple laboratory procedures. Several features aid in the differentiation between thalassemia minor and type "c" hemoglobin. Thalassemia is found mainly in persons whose racial background is Near Eastern and Mediterranean; and several cases have been found among Orientals.[14,15] To date, the type "c" hemoglobin anomaly has been reported only in Negroes. The appearance of the peripheral blood is likewise helpful in distinguishing between these conditions. Thalassemia is characterized by marked hypochromia, anisocytosis, poikilocytosis, and stippling of the erythrocytes. The cells containing type "c" hemoglobin are normochromic, show a relatively constant size and shape, and do not exhibit stippling. Figure 2 illustrates these differences. The diagnosis can be



FIGS. 2A and B. Erythrocytes of patient with homozygous type "c" hemoglobin (A) compared to those of patient with Mediterranean trait (B, see opposite page). (× 341.)

made with certainty, however, only by means of electrophoretic studies of the hemoglobin. In thalassemia the hemoglobin shows normal electrophoretic mobility,[4] whereas type "c" hemoglobin is readily identified by the marked positivity of its charge. The introduction of paper electrophoresis has placed this valuable diagnostic technic at the disposal of the routine clinical laboratory.

The type "c" hemoglobin anomaly appears to be relatively benign as compared with the sickle anomaly. In the cases where "c" hemoglobin has been reported in combination with sickle (b) hemoglobin, the resulting anemia was mild and crises were not a prominent feature of the disease.[3] In the patient reported in this paper the occurrence of "homozygous" type "c" hemoglobin in the erythrocytes was associated with a hemolytic process of such mild degree that the bone marrow was readily able to prevent manifest anemia by increasing its blood production. The occurrence of extramedullary hematopoiesis was suggested by the appearance of normoblasts in the peripheral blood. It is not yet possible to evaluate fully the possible range of damage produced by type "c" hemoglobin, as the number of such recognized cases is small. Future reports should amplify this new and intriguing problem.

The means by which type "c" hemoglobin causes damage to the erythrocytes is not clear. Target cells are the outstanding morphologic manifestation of the presence of this pigment. These cells appear to represent a condition in which there is an excessive surface/volume relationship.[13] This is usually accompanied by increased resistance to hypotonic hemolysis, and possibly a greater liability to mechanical fragmentation. The patient's erythrocytes did not show a significant increase in mechanical fragility on the basis of an *in vitro* test. Such studies are not necessarily a reflection of cell behavior in the body, and may not reflect the ability of the cell to withstand physiologic adversities which cannot be duplicated by available technics. The linear but accelerated disappearance of the patient's erythrocytes in a normal subject indicates that all cells were uniformly

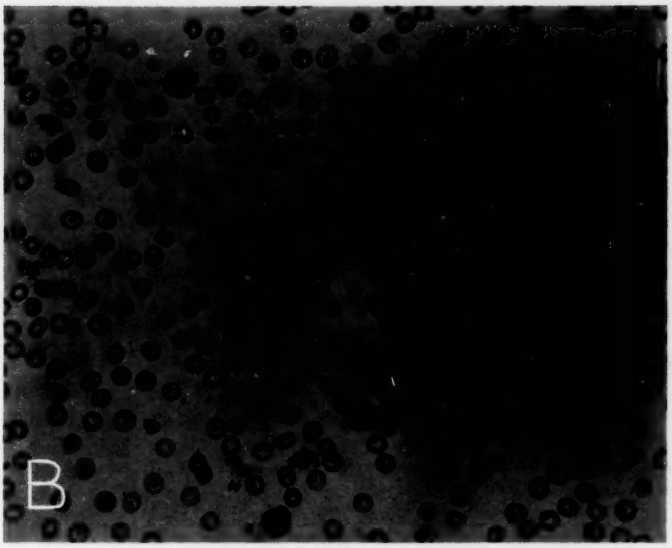


FIG. 2B. (× 341.) For legend, see opposite page.

affected, whatever the mechanism by which the abnormal hemoglobin is related to impaired erythrocyte survival.

As is the case with the other known abnormal hemoglobins, the hereditary transmission in the present situation appears to have followed mendelian principles. The patient was "homozygous" with respect to "c" hemoglobin; the father was a carrier. The mother must likewise be presumed to harbor "c" hemoglobin, although unfortunately she was not available for study.

SUMMARY

A case of "homozygous" type "c" hemoglobin is reported in a Negro child. Although the patient was clinically free of hemolytic disease, the peripheral blood showed numerous target cells, and a compensated hemolytic process was demonstrated. Clinical and theoretic implications of the condition are discussed.

REFERENCES

1. Pauling, L., Itano, H. A., Singer, S. J., and Wells, I. C., Sickle cell anemia, molecular disease, Science 110:534, 1949.
2. Kaplan, E., Zuelzer, W. W., and Neel, J. V., New inherited abnormality of hemoglobin and its interaction with sickle cell hemoglobin, Blood **6**:1240, 1951.
3. Itano, H. A., Third abnormal hemoglobin associated with hereditary hemolytic anemia, Proc. Nat. Acad. Sc. **37**:775, 1951.
4. Spaet, T. H., Identification of abnormal hemoglobins by means of paper electrophoresis, J. Lab. & Clin. Med., to be published.
5. Singer, K., Chernoff, A. I., and Singer, L., Studies on abnormal hemoglobins. I. Their demonstration in sickle cell anemia and other hematological disorders by means of alkali denaturation, Blood **6**:413, 1951.
6. Watson, C. J., Studies on urobilinogen. I. Improved method for quantitative estimation of urobilinogen in urine and feces, Am. J. Clin. Path. **6**:458, 1936.
7. Mills, S. D., and Mason, H. L., Values for fecal urobilinogen in childhood, Am. J. Dis. Child. **84**:322, 1952.

8. Wintrobe, M. M., Clinical Hematology, Philadelphia, Lea & Febiger, 1951.
9. Ashby, W., Determination of life of transfused blood corpuscles in man, J. Exper. Med. **29**:267, 1919.
10. Davis, W. D., and Arrowsmith, W. R., Effect of repeated phlebotomies in human hemachromatosis, J. Lab. & Clin. Med. **39**:526, 1952.
11. Crosby, W. H., and Akeroyd, J. H., Limit of hemoglobin synthesis in hereditary hemolytic anemia: Its relation to excretion of bile pigment, Am. J. Med. **13**:273, 1952.
12. Singer, K., Pathogenesis of sickle cell anemia, Am. J. Clin. Path. **21**:858, 1951.
13. Crosby, W. H., Pathogenesis of spherocytes and leptocytes (target cells), Blood **7**:261, 1952.
14. De Marsh, Q. B., Severe Mediterranian anemia (Cooley's anemia) in Chinese child, Blood **5**: 798, 1950.
15. Silverberg, J. H., and Shotton, D., Mediterranean anemia (hereditary leptocytosis) in Chinese family, New England J. Med. **245**:688, 1951.

SPANISH ABSTRACT

Hemoglobina c de Tipo Homocigótico: Presentación de un Caso

De 1949 a la fecha, después de que Pauling y sus colaboradores informaron de la anormal movilidad electroforética de la hemoglobina de enfermos con anemia de células en hoz, dos nuevas hemoglobinas, también anormales, han sido descritas; una llamada tipo III, con actividad en el campo electroforético como partícula positiva más potente que la hemoglobina normal y la de la anemia de células en hoz; la otra semejante a esta última pero de mayor solubilidad en su forma reducida y sin capacidad de alterar los glóbulos rojos. A estas cuatro variedades de hemoglobina, Itano las ha designado a,b, c y d, correspondiendo respectivamente a la normal, a la de células en hoz, al tipo III y a la última mencionada en las líneas anteriores. Hasta hoy no se han reportado en forma pura ni el tipo c ni el d en los eritrocitos de enfermos pero sí en combinación con los pigmentos a y b.

El presente artículo se refiere a un paciente con hemoglobina que electroforéticamente puede considerarse como tipo puro c, negrito de cuatro años de edad que se hospitalizó por la presencia inexplicable de un hematoma en la región temporal izquierda de iniciación en las regiones periorbiculares. Los antecedentes familiares y personales del niño no dieron datos sugestivos de enfermedad hemolítica; el niño mismo aparecía normal y sólo el examen de sangre periférica mostró al principio leucocitosis con neutrofilia, posteriormente con linfocitosis, y la instalación de una anemia discreta y transitoria cuya característica fundamental fué la presencia de numerosas células en tiro al blanco y normoblastos persistentes en pequeño número; la médula ósea mostró ligera hiperplasia eritrocítica y la ausencia de hipocromia. La hemoglobina homocigótica tipo c se identificó por electroforesis y el proceso hemolítico por aumento de urobilinógeno fecal y la disminución en la vida de las glóbulos rojos del paciente; la hemolisis se compensó por superproducción eritroblástica. Se supone que hay posibilidad de trastornos potenciales como la formación de cálculos biliares, crisis de anemia, etc.

Los autores hacen algunas consideraciones sobre el diagnóstico diferencial de los cuadros con células en tiro al blanco, pues en ellos debe diferenciarse también la hemoglobina c. Crosby los clasificó en cinco grupos: el que se asocia a la deshidratación, el consecutivo a una esplenectomía, el que se encuentra en enfermedades hepáticas, el de la anemia en células en hoz y el de algunas hipocromias principalmente de la talasemia. De todos ellos, sólo este último cuadro presenta problema diagnóstico ya que los demás tienen signos clínicos o de laboratorio característicos. A pesar de tener particularidades propias tanto la talasemia como la anemia con hemoglobina tipo c, su diferenciación puede realizarse con seguridad sólo por estudios electroforéticos de la hemoglobina, que dan movilidad normal para la primera y marcadamente positiva en su carga para la de tipo c.

Las anomalías de pacientes con hemoglobina tipo c son relativamente benignas, inclusive al asociarse a la anemia de células en hoz (hemoglobina b); sin embargo, las posibilidades lesivas de este tipo de hemoglobina no se pueden valorar todavía en vista de los pocos casos observados. Tampoco es muy clara la manera de actuar de esta hemoglobina c en la producción de trastornos en los eritroblastos. La transmisión hereditaria parece seguir las leyes mendelianas; en este caso el paciente era homocigótico en relación a la hemoglobina c, siendo el padre portador. Se supone que la madre albergaría la hemoglobina c aun cuando desgraciadamente no pudo ser estudiada.

2398 Sacramento Street

PERSISTENCE AND DISTRIBUTION OF TOXOCARA LARVAE IN THE TISSUES OF CHILDREN AND MICE

By MARGARET H. D. SMITH, M.D., AND PAUL C. BEAVER, PH.D.
New Orleans

RECENTLY three cases of extreme eosinophilia, associated with eosinophilic granulomatous lesions of the liver, were studied by Beaver, Snyder et al.[1] In one of the three, a biopsy specimen of the liver contained a larval nematode which was recognized as a species of the genus Toxocara, either T. canis or T. cati, common ascarids of dogs and cats, related to Ascaris lumbricoides, which commonly infects man. These authors proposed the designation visceral larva migrans for the syndrome, by analogy with the term "cutaneous larva migrans" (creeping eruption), which is applied to the skin infection produced in human beings by hookworms of nonhuman origin.

The recognition that Toxocara larvae are the apparent cause of a human disease raised the following questions: 1. Can it be shown experimentally that the larvae of T. canis hatch in the human intestine, with subsequent invasion of the viscera and production of chronic eosinophilia? 2. Is invasion limited to the liver and lungs, or are larvae likely to be found in other tissues? 3. How long may living larvae persist in the tissues?

In an attempt to elucidate these problems, the following investigations were undertaken:

A. Administration of a calculated dose of Toxocara canis larvae to mentally defective children, with follow-up studies for 13 months.

B. Administration of a similar dose of Toxocara canis egg to a group of mice, which were killed at intervals thereafter, and examined for presence of nematode larvae in the brain, lung, liver, spleen, heart.

EXPERIMENTAL RESULTS

A. Administration of T. Canis Larvae to Children: Two mentally defective infants, shown to be free of intestinal parasites, were each infected by the oral route with 200 embryonated eggs of Toxocara canis. The infectivity of the eggs and the longevity of the larvae in animal tissues were simultaneously demonstrated by administering 200 eggs of the same batch to mice.

Patient A was a 2 year old Negro female with decerebrate rigidity as a result of meningitis. She was known to have had ascariasis (Ascaris lumbricoides) previously but her infection had terminated two months prior to the present investigation. During the three weeks following infection with Toxocara, her rectal temperature rose to 37.8°C. on five different days, but there was never any recognizable hepatomegaly, pulmonary infiltration or other manifestation of ill health. The eosinophils in her peripheral blood, which prior to infection had ranged between 0% and 3% rose within one month to 52%, with total leucocyte count varying between 17,000 and 24,500 cells per mm.^{3} Thereafter there

From the Departments of Tropical Medicine and Public Health, Pediatrics, and Microbiology, Tulane University, New Orleans.

(Received for publication June 3, 1953.)

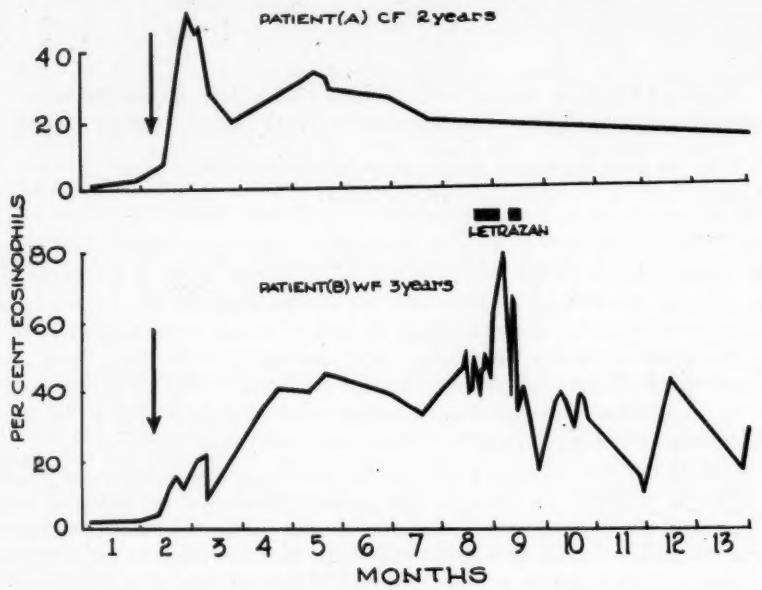


CHART 1. Eosinophilia over 13 mo. period in 2 patients following ingestion of 200 Toxocara canis egg (indicated by arrow). In Patient B hetrazan® administration during 8th to 9th mo. of infection produced marked fluctuation in eosinophil count.

was a gradual irregular decline, as shown in chart 1. At the time of the last observation, 13 months after infection, there were still 15% eosinophils.

Patient B was a 3 year old child with a severe congenital cerebral defect as well as minimal mediastinal tuberculosis. She also was fed 200 Toxocara canis eggs. The edge of her liver became just palpable during the ensuing month, but she ate and gained as usual. Neither fever nor pulmonary infiltration was detected at any time. The eosinophils, which prior to infection represented 3 to 6% of her total leucocyte count, rose within one month to 20% of 9,500, and by the end of 3 months to 45% of 22,500 leucocytes/mm^3. After six months, a leucocytosis of 34,600 was noted, with 42% eosinophils, and similar figures were obtained 10 months after infection. At the end of a year the eosinophils still fluctuated between 17 and 31% with a total leucocyte count of approximately 18,000 (chart 1). Serum proteins determined just prior to infection were 6.85 gm./100 cc. and six weeks after infection 8.2. Two courses of hetrazan® (1-diethylcarbamyl-4-methyl piperazine hydrochloride) administered to this child resulted each time in a noticeable rise in the eosinophil count within a few days, followed by a sharp fall and a quick return to the pretreatment levels.

Stools of both patients were examined repeatedly after infection but no eggs or immature worms were ever found. Spinal fluid findings were never abnormal, nor were any bone or sense organ lesions detectable on roentgenographic examination or otherwise.

B. Administration of Toxocara Canis Eggs to Mice: Methods—Fifteen white mice obtained from a local mouse colony were employed in the experiment. Each was given 200 infective eggs by stomach tube. The mice were killed singly at intervals up to one

year. In some the total number of larvae was counted according to the method of Sprent,[2] after macerating the tissues and digesting with pepsin. Organs from other mice were fixed, sectioned and stained for microscopic examination.

The mice killed within two weeks of infection showed abundant larvae in the liver, lungs and kidneys, also many in the muscles and brain, whereas in those killed 1 to 6 months after infection, the majority were in the brain and muscles. The mouse killed 10 months after infection* yielded a total of 152 living larvae: 120 from the brain, 17 from the liver and 15 from the carcass, as well as several cysts containing dead larvae and other cysts in which the larvae had presumably been destroyed. The most interesting information was afforded by the mouse killed after one year. During the last two weeks of life, this mouse became paralyzed. When it was killed, therefore, the brain and spinal cord, though they showed no gross lesions, were fixed *in toto* for microscopic study. The remaining organs were digested and the number of larvae counted: 32 living larvae were found free in the tissues, also 27 encapsulated ones; 16 encapsulated dead larvae; and 13 cysts in which larvae had apparently been destroyed. Thirty transverse sections 7 μ in thickness were cut from each of three levels in the brain (frontal lobes, thalamus and pons); they were found to contain 15 complete larvae and portions of 13 others. Since collectively these 90 sections represented only about one twentieth of the brain, a large proportion of the larvae in this mouse were undoubtedly in the brain.

Microscopic examination of the liver revealed in the mice early focal accumulations of leucocytes and macrophages, as previously described by Hoeppli, Feng and Li.[4] On the other hand examination of brain sections from mice killed 10 months and one year after infection showed much less striking lesions. In fact in the immediate vicinity of the larvae in these brains, nothing abnormal was noted at all, except for physical displacement of tissue elements by the worms themselves, and, in a single area, questionable gliosis. In the cerebellum there were a few scattered foci of recent and earlier minute hemorrhage, manifested by hemosiderosis and slight perivascular inflammation.

Discussion

There have been a few questionable records of T. canis developing to their adult stage in man. The present experiment adds doubt to these reports. However T. cati, which is similar to T. canis in all other known respects, has been reported in the adult stage in man 18 times.[5]

The authors' observations further confirm the other available evidence for the hypothesis that infective Toxocara canis larvae are able to invade the tissues of children. The choice of 200 larvae as a dose that would be safe and at the same time would produce clearcut manifestations of infections was based on the following considerations: studies by Headlee[6] and Beaver[7] had shown that T. canis eggs occur abundantly in some dooryards, indicating that children may ingest several hundred eggs in relatively small quantities of the soil. These and other studies on the epidemiology of human ascariasis had further shown that ascariasis is essentially a household infection acquired in most instances by the ingestion of dooryard soil.[8-10] Therefore it seemed reasonable to assume that the

* Between 8 and 10 mo. after infection the mice were poorly attended and 3 either escaped or died. At least one died and was partly eaten by the 2 survivors. Thus the larvae recovered from the 2 mice examined at 10 and 12 mo., respectively, were probably not all derived from the initial infection with 200 infective eggs, since Nichols[3] has shown that T. canis larvae eaten with infected mouse tissue will penetrate the intestinal wall and invade the tissues of a second mouse.

ingestion of as many as 200 Toxocara eggs might be a natural and frequent occurrence. Also the number of lesions found in the liver and the frequency with which larvae had been found in small biopsy specimens indicated that in the more seriously affected children several thousand larvae had been eaten.

It is further apparent from this experiment that, in some instances at least, as many as 200 larvae may be well tolerated and that the visceral larva migrans syndrome in its more extreme forms must result from much higher dosage of larvae, from greater host sensitivity to the parasites, or possibly in some cases from other species of larvae more damaging than those of Toxocara.

The eosinophilia observed in the two children was interpreted as being caused by the T. canis larvae. Since the eosinophil levels remained relatively high for one year, the authors believe that some of the larvae probably survived for that period or longer. Observations on experimental infections in mice yield evidence that larvae do survive for such a period of time. The data indicate that the bone marrow responded to the infection not only with an increase in the number of eosinophilic leucocytes, but with an increased production of other types of leucocytes as well. The leucocytosis and eosinophilia seem to have been particularly intense during the first two months of the infection and continued in lesser degree for a period of at least 13 months. Of interest is the fact that the leucocytosis and eosinophilia in the second patient reached their peak months later than in the first patient. The reason for the observed difference is not to be sought in the size of the infective dose, since both children received the same number of larvae. The fact that the patient with the more rapid rise had relatively quick fall in white blood cells and eosinophils had previously suffered an infection with ascariasis may be a factor. A previous infection with Toxocara, acquired simultaneously with the ascaris, is a possibility. Another possibility for the difference in hematologic response between the two patient lies in the fact that the second child had a primary tuberculous complex at the time of her Toxocara infection. While her tuberculous lesion was producing no outward symptoms such as fever, anorexia, lymphadenopathy, an underlying tuberculous infection might well modify the reaction to a superimposed parasitic infection.

At the time when her leucocytosis and eosinophilia were at their peak, Patient B was given hetrazan®. The dosage was 150 mg. daily, divided into three doses, and continued over a period of one month, with a rest period during the third week. This drug has been used for several years in the treatment of filariasis[11] and ascariasis.[12] Previous observations on patients with filariasis[13] and with visceral larva migrans syndrome[1] suggests that a prompt rise and fall in the eosinophil count usually will accompany the administration of hetrazan®.

The relative distribution of larvae in the mice, at various intervals after infection, and particularly the high concentration in the central nervous system has been reported previously.[1] The same phenomenon has been observed in the guinea pig.[14] Convulsions, vertigo and other neurologic manifestations have long been associated by clinicians with worm infections[15–17] but, in the absence of a clearcut pathologic basis for such an association, it has currently fallen into disrepute.

The occurrence of Toxocara larvae in large numbers in the brains of infected experimental animals suggests that focal tissue damage produced by variously located larvae in children may well account for bizarre symptoms, the nature of which would depend on the number and the exact location of the parasites. In the single instance in which a nematode larva, apparently Toxocara, was found in the human brain, its discovery was due

to a macroscopic lesion in the thalamus.[18] Damaging lesions around larvae which likewise appear to be Toxocara have been observed in the human eye.[19]

On the other hand it is noteworthy that evident reaction may not be produced about the larvae in nerve tissue in the mouse brain, so that the spinal fluid might well appear entirely normal. Eosinophilic pleocytosis is a well established, but rare entity, occurring mainly in cases of cerebral cysticerosis, and occasionally with cerebral echinococcus infection.[20, 21] It has also been noted in patients who presumably did not have either of these infections, and in whom the etiology remained obscure. To date, however, the authors know of no evidence that ascariasis of any type causes abnormalities of the spinal fluid.

Perhaps the chief reason why such larvae have only once been reported in the central nervous system in man can be attributed to the usual lack of any conspicuous cellular reaction in either the meninges or the brain tissue itself. Hoeppli[22] and Yokogawa,[23] as well as Beautyman and Woolf,[18] have all commented on this fact; and in the present authors' experience it is striking.

From a practical point of view, the findings in both children and mice infected experimentally with dog ascarid larvae re-emphasize the potential dangers of dogs and cats as household pets, because of their intimate contact and at least partial interchangeability of intestinal parasites, as well as bacteria, viruses and other infectious agents.*

Summary and Conclusions

Two young mentally defective children were infected with a small number of embryonated eggs of the dog ascarid, Toxocara canis. They remained asymptomatic clinically but developed eosinophilia which persisted for more than 13 months.

Tissues from mice infected experimentally with the same dose of dog ascarid eggs were examined at intervals up to one year after infection. In the early stages of infection the larvae were found principally in the liver and lungs, but in the later stages they were most numerous in the brain.

It seems not improbable that some of the neurologic manifestations associated with ascariasis may be due to actual presence of Toxocara larvae in the tissues of the central nervous system, rather than to toxic or allergic effects of Ascaris lumbricoides.

This new evidence, added to previous observations on the effect of dog and cat ascarids in children, re-emphasizes the need for ridding household pets of their intestinal parasites at frequent intervals.

References

1. Beaver, P. C., and others, Chronic eosinophilia due to visceral larva migrans, Pediatrics **9**:7, 1952.
2. Sprent, J. F. A., On migratory behavior of larvae of various ascaris species in white mice, J. Infect. Dis. **90**:165, 1952.
3. Nichols, R. L., Morphology of infective stage larvae of Toxocara species, to be published.
4. Hoeppli, R., Feng, L. C., and Li, F., Histological reactions in liver of mice due to larvae of different ascaris species, Peking Natural History Bull. **18**:119, 1949.
5. Mendheim, H., Scheid, G., and Schmidt, J., Die selteneren Spulwurminfektionen beim Menschen, Ztschr. f. Tropenmed. u. Parasitol. **3**:368, 1952.

* Evidence presently available suggests that young dogs and cats living in close relationship with children should be "dewormed" every 4 wk.; in dogs between 6 mo. and 2 yr. of age the interval between treatments can be 6 to 8 wk. Older dogs and cats infrequently have Toxocara infections.

6. Headlee, W. H., Epidemiology of human ascariasis in metropolitan area of New Orleans, Louisiana, Am. J. Hyg. **24**:479, 1936.
7. Beaver, P. C., Observations on epidemiology of ascariasis in region of high hookworm endemicity, J. Parasitol. **38**:445, 1952.
8. Brown, H. W., Human ascaris as household infection, J. Parasitol. **13**:206, 1927.
9. Cort, W. W., Recent investigations on epidemiology of human ascariasis, J. Parasitol. **17**:121, 1931.
10. Cort, W. W., and Otto, G. F., Ascaris problem in United States, South. M. J. **26**:273, 1933.
11. Hawking, F., Some recent work on filariasis, Tr. Roy. Soc. Trop. M. Hyg. **44**:153, 1950.
12. Hoekenga, M., Treatment of ascariasis in children with hetrazan syrup, Am. J. Trop. Med. & Hyg. 1:688, 1952.
13. Santiago-Stevenson, D., Oliver-Gonzales, J., and Hewett, R. I., Treatment of filariasis bancrofti with 1-diethylcarbamyl-4-methylpiperazine hydrochloride ("hetrazan"), J. A. M. A. **135**:708, 1947.
14. Fülleborn, F., Askarisinfektion durch Verzehren eingekapselter Larven und über gelungene intrauterine Askarisinfektion, Arch. Schiffs-u. Trop. Hyg. **25**:367, 1921.
15. Bridge, E. M., Epilepsy and Convulsive Disorders in Children, ed. 1, New York, McGraw-Hill Book Company, 1949.
16. Swartzwelder, J. C., Clinical ascariasis: Analysis of 202 cases, Am. J. Dis. Child. **72**:172, 1946.
17. Keller, A. E., Casparis, H., and Leathers, W. S., Clinical study of ascariasis, J.A.M.A. **97**:302, 1931.
18. Beautyman, W., and Woolf, A. L., Ascaris larva in brain in association with acute anterior poliomyelitis, J. Path. & Bact. **63**:635, 1951.
19. Wilder, H. C., Nematode endophthalmitis, Tr. Am. Acad. Ophth. **55**:99, 1950.
20. Applebaum, I. L., and Wexberg, L. E., Eosinophilia in spinal fluid, J. A. M. A. **124**:83, 1944.
21. Sison, A. G., Campos, P. C., and Apostol, R., Eosinophilia in spinal fluid: Report of 4 cases, Acta med. Philippina **8**:95, 1952.
22. Hoeppli, R., Über Beziehungen zwischen dem biologischen Verhalten parasitischer Nematoden und histologischen Reaktionen des Wirbeltierkörpers, Beihefte z. Arch. Schiffs-u. Trop. Hyg. **31**:40, 1927.
23. Yokogawa, cited in Beautyman and Woolf.[18]

SPANISH ABSTRACT

Persistencia y Distribución de las Larvas de Toxocara en los Tejidos de Niños y Ratas

El hallazgo de larvas de T.canis o T.cati (nemátodo clasificado como especie dentro del género Toxocara y relacionado al Ascaris lumbricoide que infecta al hombre), en tejido hepático de un niño con eosinofilia acentuada sugirió a los presentes autores la idea de hacer una invetigación experimental en niños y ratas sobre el desarrollo de larvas de T.canis en el intestino, la invasión subsecuente a diversas vísceras, la producción de eosinofilia y por último, la sobrevida de tales larvas en los tejidos.

Con tal objeto se administró por vía oral una dosis definida de 200 huevecillos de Toxocara canis a dos niños con retardo mental, que se observaron durante 13 meses, y a un grupo do ratas, que se autopsiaron a intervalos determinados para buscar la presencia de larvas en cerebro, pulmones, hígado, bazo y corazón.

Los dos niños utilizados en esta experiencia, uno de la raza negra de dos años de edad y otro de la raza blanca de tres años de edad, no mostraron alteraciones en su cuadro clínico, durante el período de observación, y sí un aumento marcado del número de leucocitos y de eosinófilos a partir del primer mes de la ingestión de los huevecillos. La eosinofilia persistía 13 meses después de iniciado el estudio. Los exámenes de materias fecales nunca mostraron huevecillos o parásitos inmaduros; el líquido céfalo raquídeo fue siempre normal y la radiografía de huesos y órganos de los sentidos nunca dio datos anormales.

Las ratas mostraron abundante infiltración de larvas a las dos primeras semanas de observación, en hígado, pulmones, riñones, músculos y cerebro; desde el primero hasta el sexto mes la mayoría

se localizó en el cerebro y en los músculos; una rata muerta a los 10 meses, mostró 120 larvas vivas en el cerebro, 17 en el hígado, 15 en el esqueléto óseo y quistes de larvas muertas distribuídas en los mismos tejidos. Otra autopsiada después de un año, paralizada en sus dos últimas semanas de vida, no mostró lesiones macroscópicas en el cerebro ni en la médula espinal, pero el estudio microscópico reveló gran cantidad de larvas en cerebro y médula.

De estas observaciones los autores deducen que algunas manifestaciones neurológicas asociadas a la ascaridiasis puede deberse a la presencia real de larvas en los tejidos del sistema nervioso central más bien que a efectos tóxicos y alérgicos de la ascaridiasis. Asímismo recomiendan tanto la vigilancia de perros y gatos en las casas por su peligro potencial para los niños, en vista de la posibilidad de ser portadores de ascárides, como el tratamiento adecuado a los animales a intervalos frecuentes para impedir el contagio a los niños que jueguen con ellos.

1430 Tulane Avenue

HEMOLYTIC STREPTOCOCCAL INFECTION IN CHILDHOOD

By LOWELL A. RANTZ, M.D., MARGARET MARONEY, M.D., AND JOSEPH M. DI CAPRIO, M.D.
San Francisco

SURPRISINGLY little information is available in regard to the natural history, bacteriology, and immunology of hemolytic streptococcal disease in children although it is uncommon after adolescence in the civilian population. Powers, Boisvert, Trask and their associates[1] have coined the term "streptococcosis" to cover the whole panorama of streptococcal infection and have described three types. One, which occurs in infants and young children, is characterized by a subacute, protracted course, numerous suppurative complications, and by the absence of both skin rash and nonsuppurative complications. A second, that of middle childhood, has a sharp onset, finite course, less frequent suppurative complications, and is often accompanied by a skin rash. The third, an adult type, is similar but skin rash and suppurative complications are rare. Rheumatic fever is a common sequel to both of the latter forms of streptococcal disease.

No other comprehensive descriptions of the natural history of hemolytic streptococcal infection in childhood have appeared. Particularly lacking has been a study of these disorders in outpatients. The study described above was conducted largely in a hospital and, for this reason, emphasized the most severe manifestations of streptococcal illness.

A four year continuing investigation of hemolytic streptococcal infection in childhood was undertaken to obtain additional information about this important subject. Suitable cases were discovered by the application of clinical and bacteriologic methods to individuals in the outpatient clinic who presented symptoms of respiratory infection or by the serial study of infants followed from birth. Hospitalized children were not included.

Three previous papers have described the frequency of streptococcal infection and reinfection in various age groups and certain aspects of the immunology of these disorders in childhood.[2-4] This report describes the clinical manifestations of streptococcal infection during the first eight years of life.

MATERIALS AND METHODS

Clinical Material.—Infants and children attending the Pediatric Out-Patient Clinics of Stanford University Hospitals were studied. The composition of the several groups will be described in the appropriate sections of this report. Detailed studies were frequently undertaken in which serial clinical, clinicopathologic, bacteriologic and immunologic observations were made.

Penicillin Therapy.—Penicillin was administered in certain cases in standard courses consisting of daily injections of 300,000 units of procaine penicillin in aqueous suspension for 5 consecutive days, or of 3 doses at 48 hr. intervals of the same amount of the drug suspended in oil and 2% aluminum monostearate. Oral or local administration was occasionally utilized.

From the Departments of Medicine and Pediatrics, Stanford University School of Medicine, San Francisco.

This investigation was conducted under the auspices of the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, aided by a grant from the Life Insurance Medical Research Fund, and supported in part by a research grant from the National Heart Institute of the National Institutes of Health, United States Public Health Service.

(Received for publication April 30, 1953.)

Bacteriologic Studies.—Cotton-tipped wood swabs were passed through the mouth and rubbed over the tonsils and nasopharynx under direct vision. Controlled studies revealed that the passage of wire swabs through the nose was an unsatisfactory technic for the recovery of group A streptococci from this area. Materials were obtained from the nose by inserting wire swabs approximately 3 cm. into the nasal ostia, and from the ears and skin in the usual way.

Swabs obtained from acutely ill patients were streaked on two 10% horse blood agar plates. One was prepared as a "streak pour plate," and incubated for 18 hr. Swabs obtained at follow-up examinations were similarly treated and, in addition, were often enriched by the method of Pike.[2] Isolated hemolytic streptococci were grouped and typed by precipitin technics.[6] * Strains were recovered frequently which could not be typed.

Antistreptolysin O.—The concentration of antistreptolysin O in the collected sera was measured by a method previously described.[7]

Clinicopathologic Studies.—The formed elements of the blood were counted by standard methods. Hemoglobin was estimated with the Haden-Hausser microhemoglobinometer, and the erythrocyte sedimentation rate with the Clay-Adams micro-apparatus.

First Four Years of Life

Streptococcal Infection in Children Followed Serially from Birth

Between April and December of 1947 a large number of newborn infants were enrolled in a group to be subjects of continuing study. The parents of all were strongly urged to bring the children to the clinic whenever a respiratory infection was present.

TABLE 1

Frequency of Infection and of Clinical Recognition of Infection by Hemolytic Streptococci in Infants Followed Serially from Birth

	Follow-up Period			
	1	2	3	4
Mean age (mo.)	15.5	24.3	31.3	47.9
No. of subjects	92	70	52	29
No. of infections in previously uninfected	28	8	5	7
No. of reinfections	0	9	4	4
Total infections	28	17	9	11
No. of infections recognized clinically	4	0	2	3
Per cent of infections recognized clinically	14.7	0.0	22.2	27.2

Cooperation, especially during the first two years, was good. In addition the subjects were recalled at irregular intervals for examination and bacteriologic and immunologic investigation. The collected data have been analyzed in periods based on the time of routine follow-up. Many children had been seen in the intervals. Pertinent data as summarized from a previous report[2] are presented in table 1.

Infection of the previously uninfected occurred at a rate of from 20 to 25 per 100 per annum. Reinfections were discovered at a rate of about 50 per 100 per annum. Infection or reinfection was recognized in 86% of the cases only by isolation of the organism from the nasopharynx and demonstration of a significant increase in circulating serum antistreptolysin O since the illness, if any, did not come under clinical observation. There were 28 strains of Group A, 6 of Group C, and 6 of Group G.

Only 9 of 65 of the streptococcal illnesses associated with tissue invasion and antibody

* Sera were supplied by the United States Public Health Service Communicable Disease Center, Chamblee, Ga.

production were regarded by the parents as sufficiently severe to require the advice of the clinic physicians. Nine per cent of the infections in children less than 24 months of age, and 25% of those occurring between 24 to 48 months of age, were studied clinically. Six of these were initial and 3 were reinfections. Careful questioning revealed only an occasional illness in the remaining 54 which could be recognized as streptococcal. Two with bacteriologic and immunologic evidence of streptococcal infection had had "sore throats" a few weeks before a clinic visit. All had had frequent "colds" and other minor respiratory infections from which they had recovered within reasonable periods after the use of home remedies. Seventeen children had had nonstreptococcal disease sufficiently severe to require definitive therapy. These included 12 episodes of purulent otitis media 4 of tracheobronchitis or pneumonia requiring hospitalization, and one of meningococcemia. Ten of the 12 examples of otitic infection were in children less than 15 months of age.

The 4 illnesses occurring during the first 15 months of age that were studied in detail were examples of typical infantile streptococcal disease. All were indolent* and rhinorrhea was the predominant early symptom. The patients were brought to the clinic in each instance after a suppurative complication had appeared. In one this was otitis media which developed after about six weeks of low grade respiratory infection. Suppurative cervical adenitis developed in two others after one and three weeks of a similar disease. A fourth child exhibited extensive hemolytic streptococcal pyodermia associated with eczema at 6 months and again at 31 months of age without definite evidence of respiratory infection although large numbers of the infectious agent were present in the throat during each episode.

Clinically recognized infections were not seen during the period from about 15 to 30 months of age. Five occurred after this age, one of which has been mentioned above. The other children were 31, 43, 48 and 53 months old at the time of the illness. They all presented signs of the adult type of streptococcal disease with sore throat, swollen tonsils, red throat, and tender anterior cervical glands. Tonsillar and pharyngeal exudate was not described, nor was there a skin rash in any case. The illness in these cases was more acute with fever and prostration, so that 4 of the 5 came to the clinic shortly after onset and received penicillin. The other was seen somewhat later and was not treated. Suppurative complications did not occur in any case.

Clinically Recognized Streptococcal Infection

A disease believed to be a group A streptococcal infection was recognized in 55 children less than 4 years of age by clinical, bacteriologic and immunologic screening procedures applied to the outpatient clinic population presenting signs of respiratory infection and pyodermia.

Nine recent infections in eight children were established by the isolation of group A streptococci from the nasopharynx and by the subsequent increase in serum antistreptolysin O. They have not been included in this analysis since it was impossible to be certain that the respiratory illness which brought them under observation was streptococcal disease. All of them had symptoms of the common cold or of laryngitis, tracheitis or bronchitis. It was likely that a mild or inapparent streptococcal infection had occurred at about the same time as the nonbacterial infection. An additional 11 cases have been excluded because of inadequate clinical data although all were almost certainly examples of streptococcal disease.

* The term, as used throughout this paper, refers to an illness without a sharp finite onset and with a subacute protracted course. Fever was usually absent or low grade.

TABLE 2

GENERAL NATURE OF HEMOLYTIC STREPTOCOCCAL INFECTION AND REINFECTION IN CHILDHOOD

	Age at Time of Initial Infection (mo.)				
	0–12	13–24	25–48	49–72	72–96
Total patients	13	20	22	23	20
Mean age at first infection	7.5	15.9	35.9	60.4	86.7
Total infections clinically recognized	13	25	24	30	25
Nature of Clinical Illness					
Initial Infections					
Nasopharyngitis only	2	4	4	16	13
Suppurative otitis media	8	12	6	3	2
Suppurative lymphadenitis	—	2	2	1	1
Pyodermia	2	3	10	3	3
Vaginitis	—	—	—	—	1
Reinfections					
Nasopharyngitis only	—	2	—	5	3
Suppurative otitis media	1	—	—	—	—
Suppurative lymphadenitis	—	—	—	—	—
Pyodermia	—	2	2	2	1
Vaginitis	—	—	—	—	1
Reinfection not recognized clinically	6	4	13	6	4
Total reinfections	7	8	15	13	9

General Information: Data in regard to the general nature of the initial disease and of 20 reinfections are presented in the first three columns of table 2. The study described in the last section indicated that group A streptococcal infection occurs frequently in early childhood but is rarely severe enough to demand medical care in the absence of suppurative complications. The present group of cases emphasizes these facts. Such complications were present in 44 of the 55 initial infections. Twenty-seven had suppurative otitis media, 13 had pyodermia and 4 had suppurative cervical adenitis. Disease limited to the nasopharynx was present in only 11 cases. Many of these patients were followed for long periods of time during which reinfection took place. More than half of these new tissue reactions to streptococcus were either inapparent or insufficiently severe to require clinic attendance and were demonstrated only by application of bacteriologic and immunologic methods. Three-quarters of the new illnesses with clinical signs presented suppurative complications. A higher percentage of these involved the skin than did the initial illnesses. No other discernible differences between the two groups were noted.

Onset and Early Symptoms: Clinical information in regard to the onset and predominant early symptoms of hemolytic streptococcal respiratory disease in children less than 4 years of age is presented in table 3 based on an analysis of 55 illnesses and excluding reinfections.

The disease began with an acute febrile episode in only 7% of the group. There was no well defined incident which marked the onset in the others. Rhinorrhea was the principal early symptom in 80% of the cases in which any respiratory manifestations were observed. The parents regarded nearly all of these infections as common colds until a suppurative complication supervened. Since the advice of the clinic was not sought until after the first week (see table 4) in most cases, it is not possible to be certain that the

TABLE 3

NATURE OF ONSET AND PREDOMINANT EARLY SYMPTOMS OF HEMOLYTIC STREPTOCOCCAL RESPIRATORY INFECTION IN CHILDHOOD

Age of Patient (mo.)	Onset		Predominant Early Symptoms			
	Acute Febrile	Indolent	Rhinorrhea	Sore Throat	U.R.I.*	No Respiratory Symptoms
1 to 24†	1	32	22	0	5	5
25 to 48†	3	19	14	2	1	5
49 to 72	19	11	9	17	0	4
72 to 96	12	13	3	15	0	7

* Refers to various nondescript symptoms referable to the upper respiratory tract.
† Reinfections not included.

TABLE 4

TEMPORAL RELATIONSHIPS BETWEEN ONSET OF RESPIRATORY ILLNESS, FIRST CLINIC VISIT, AND APPEARANCE OF PRINCIPAL SUPPURATIVE COMPLICATION

Disease and Age of Subject	Total Cases	First Clinic Visit in Days After Onset of Respiratory Illness						Appearance of Principal Complications in Weeks After Onset of Respiratory Illness				
		No Resp. Illness	1–7	8–14	15–21	22–28	29+	1–7	7–14	15–21	22–28	29+
Nasopharyngitis only												
1–24 mo.	6	—	1	2	—	2	1	—	—	—	—	—
25 to 48 mo.	4	—	1	1	2	—	—	—	—	—	—	—
49 to 72 mo.	21	—	17	2	2	—	—	—	—	—	—	—
72 mo. and over	16	—	13	2	—	1	—	—	—	—	—	—
Suppurative Otitis Media												
1 to 24 mo.	20	4	1	1	7	2	5	7	1	5	2	1
25 to 48 mo.	6	—	2	1	2	—	1	3	1	1	1	—
49 to 72 mo.	3	1	1	—	—	—	1	1	1	—	—	—
72 mo. and over	2	1	—	1	—	—	—	1	—	—	—	—
Suppurative Cervical Adenitis												
1 to 24 mo.	2	—	—	—	—	1	1	—	—	—	2	—
25 to 48 mo.	2	—	1	—	1	—	—	2	—	—	—	—
49 to 72 mo.	1	—	—	—	1	—	—	—	1	—	—	—
72 mo. and over	1	1	—	—	—	—	—	—	—	—	—	—
Pyodermia												
1 to 24 mo.	5	1	1	1	1	—	1	1	1	1	1	—
25 to 48 mo.	10	5	—	1	1	2	1	1	1	2	1	—
49 to 72 mo.	5	3	—	1	1	—	—	1	1	—	—	—
72 mo. and over	4	3	—	—	—	—	1	—	1	—	—	—
Vaginitis												
1 to 24 mo.	—	—	—	—	—	—	—	—	—	—	—	—
25 to 48 mo.	—	—	—	—	—	—	—	—	—	—	—	—
49 to 72 mo.	—	—	—	—	—	—	—	—	—	—	—	—
72 mo. and over	2	2	—	—	—	—	—	—	—	—	—	—
All Infections												
1 to 24 mo.	33	5	3	4	8	5	8	8	2	6	3	1
25 to 48 mo.	22	5	4	3	6	2	2	6	2	3	2	—
49 to 72 mo.	30	4	18	3	4	—	1	2	3	—	—	—
72 mo. and over	25	7	13	4	1	—	—	1	1	—	—	—

1 to 48 mo. old—Reinfections not included.

rhinorrhea in these cases was streptococcal in origin. Large numbers of hemolytic streptococci were present in the nasal discharges of 19 of 20 cases that were studied on their first clinic visits.

Only two cases presented the symptom of sore throat usually associated with streptococcal infection in older persons. In a few there were nondescript respiratory symptoms and, in 10, a suppurative complication appeared without any preceding respiratory illness. One began with diarrhea. Gastrointestinal symptoms were notably lacking in the others.

Onset of Complications: The indolent and low grade course of these infections is further emphasized by the data in table 4. The time of onset of suppurative complications after the first signs of illness (usually rhinorrhea) was distributed rather evenly over a four week period if the 10 cases in which such a complication initiated the illness were excluded. Infection of the middle ear occurred quite early, or after the second week. Few children were seen in the clinic until a suppurative complication had appeared. Even this event did not dictate the need for immediate medical care. Thus otitis media was definitely present in the first week in 14 cases, only seven of which were seen in the clinic before the 10th day of illness. These delays reflect, in part, the cultural and educational level of the patients in the study group but also emphasize the clinically benign course of hemolytic streptococcal respiratory infection during the first few weeks in young children.

Physical Signs: It is not profitable to discuss in detail the physical signs of early hemolytic streptococcal respiratory infections in young children since only a few of these patients were seen during the first week. When they presented themselves at the clinic the predominant signs were usually those pertaining to the complicating otitis media, adenitis, or pyodermia. These could be identified very simply by appropriate examination. The temperature was normal (47%), or not greater than 37.8°C. (18%), in 65% of the whole group. The four children with suppurative lymphadenitis were all febrile. Doubtless many of those with otitis media had been so before spontaneous rupture of the ear drum and drainage occurred. No child was seen before this event. Only 14% of all the cases had temperatures as great as 38.8°C. Rhinorrhea was frequently present (see table 5). The nasal discharge was sometimes frankly purulent but often was described as "mucus" and yet contained large numbers of hemolytic streptococci.

The nasopharynx did not exhibit signs of diagnostic value. Exudative tonsillitis was never present. The tonsils were large in many instances but it was difficult to determine on the initial examination whether this was the result of infection since this is a normal condition in many healthy children. Pharyngeal edema was rarely present but diffuse red-

TABLE 5

FREQUENCY OF CERTAIN PHYSICAL SIGNS IN HEMOLYTIC STREPTOCOCCAL RESPIRATORY INFECTION IN CHILDHOOD

Age (mo.)	Total Cases	Exudate	Tender Cervical Adenitis	No Exudate or Tender Adenitis	Rhinorrhea	Scarlatiniform Skin Rash
1 to 48	40*	—	14	26	30	—
49 to 72	18†	9	10	6	11	2
72 and over	13†	8	7	3	4	2

* Includes all cases within disease limited to the respiratory tract.

† Includes only cases examined within 6 days of onset and with disease of the respiratory tract.

TABLE 6

LABORATORY DATA IN HEMOLYTIC STREPTOCOCCAL INFECTION IN CHILDHOOD: CASES STUDIED BEFORE INSTITUTION OF ANTIMICROBIAL THERAPY

	Age (mo.)	Total Cases	Total Leucocyte Count in cells/cmm.					Hemoglobin gm./100 cc.				Erythrocyte Sedimentation Rate in mm./hr.				Follow-up Observations*	
			<8,000	8,000 to 12,000	12,000 to 17,000	17,000 to 22,000	22,000+	<9	9 to 10.9	11 to 12.9	13+	<12	15 to 25	26 to 35	36+	Hemoglobin—No. of Patients with Increase of 1.0 or more gm.	Erythrocyte Sed. Rate—No. of Patients with Rate Greater than 15 mm./hr.
Nasopharyngitis	1–48	8	1	3	2	2	—	1	7	—	—	1	4	3	—	6	4
	49–96†	24	6	5	7	4	2	—	2	17	5	8	13	3	—	—	5
Suppurative otitis media	1–48	19	2	7	6	3	1	3	13	3	—	6	5	6	2	8	5
	49–96†	3	1	1	1	—	—	—	1	2	—	1	1	1	—	1	—
Suppurative lymphadenitis	1–48	2	—	—	—	—	2	—	1	—	1	—	—	2	—	—	—
	49–96†	2	2	—	—	—	—	—	1	1	—	—	—	2	—	—	1
Pyodermia	1–48	12	5	3	3	1	—	—	8	4	—	8	2	1	1	6	—
	49–96†	7	2	4	1	—	—	—	5	2	—	2	3	2	—	4	3
Vaginitis	1–48	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	49–96†	2	2	—	—	—	—	—	—	2	—	2	—	—	—	—	—

* Three to 4 wk. after institution of therapy.

† Cases with acute onset included only if data obtained during 1st 5 days of illness.

ness of this area was a quite constant finding. This is a highly subjective sign and its interpretation depends on the experience of the observer. Its presence or absence was not particularly helpful in distinguishing between streptococcal and nonstreptococcal disease among these children.

The presence of tender anterior cervical lymphadenitis has proved to be a valuable aid for the recognition of streptococcal respiratory disease in young adults. This sign was present in 14 of the 40 cases with symptoms and complications limited to the respiratory tract. A swollen gland was fluctuant in four cases. Large, readily palpable nodes that did not diminish in size during convalescence were present in many other cases. They were doubtless examples of the general lymphoid hypertrophy which is common in small children. It was extremely difficult in many cases to determine whether tenderness was present because of the age of the subjects.

A skin rash of the scarlatinal type was never observed. Pyodermia was present in 15 cases and was of the type usually described as "impetiginous."

Laboratory: Large numbers of group A hemolytic streptococci were recovered from the purulent discharges and/or the nasopharynx in all of the cases described in this and the following sections. Serologic typing of all the strains that were recovered was done. It is not profitable to display the information obtained[3] since more than 50% could not be typed.

Miscellaneous clinical laboratory data derived from observations in 41 cases in which complete studies were made shortly after recognition of the streptococcal infection in the clinic are presented in table 6. All had active disease at the time although many, particularly those with otitis media, had passed the peak of the illness.

Half of the patients with nasopharyngitis and otitis media, and one-third of those with dermatitis, had total leucocyte counts greater than 12,000/cmm. The number of cells was very high in both cases of suppurative adenitis in which the examination was made at an appropriate time.

The hemoglobin was low in nearly all of the children, only 14% having had more than 11 gm./100 cc. blood. This was partially the result of the age of most of the subjects since the normal values in this group would have been less than 12 gm./100 cc. in those 24 months of age or less, and less than 12.5 gm./100 cc. in the remainder. The nutritional status of many was also inadequate. That the streptococcal infection was principally responsible for the anemia is indicated by the fact that an increase of 1 gm. or more, with a mean of 1.5 gm., of hemoglobin/100 cc. followed the institution of antimicrobial therapy in 20 of 32 children in whom the initial level was 11 gm. or less. This increment was attained by the time of the examination approximately three weeks after treatment was started.

The erythrocyte sedimentation rate was elevated (>15 mm./hour) in 75% of cases with nasopharyngitis, adenitis and otitis media, but in only one-third of those with pyodermia. A decline to rates of less than 15 mm./hour occurred in 65% previously elevated within three weeks after treatment was begun. Several others attained normal levels within six weeks.

Electrocardiograms were obtained when a child was admitted to the study group and approximately 10 and 21 days later. None presented significant abnormalities.

Course: The previous sections have indicated the indolent course of hemolytic streptococcal respiratory infection in these young children before they appeared at the clinic. Many cases, including nearly all who had adenitis, otitis media or pyodermia, were treated

on or shortly after the first visit with systemically or locally administered penicillin. A few received a sulfonamide. This therapy so altered the course that further discussion of the natural history of these illnesses under observation is unprofitable.

Nonsuppurative Complications: Evidence of a nonsuppurative complication such as rheumatic fever or glomerulonephritis was sought by detailed serial clinical study, including ECGs, over a period of 35 days or more in all of these cases. None was discovered. Permanent recovery was exceedingly prompt when the suppurative phase was terminated by the administration of penicillin. Arthritis, late fever, late abnormalities of the electrocardiogram, or nephritis did not occur, although only about 30% received penicillin therapy during the first week and only a few before the fifth day.

Treatment: Treatment of hemolytic streptococcal respiratory infection in children less than 5 years of age with penicillin was most satisfactory. Within a short time after the parenteral administration of the drug the etiologic agent had disappeared from the nasopharynx and from the nasal, otitis or dermal discharges, and prompt recovery occurred. Improvement in general status was often dramatic and was particularly gratifying in patients who had had a long, debilitating illness. Virtually complete recovery was often seen within 48 hours after the onset of therapy. The routine which assured bactericidal concentrations of penicillin for 6 to 8 days was effective in that clinical relapse did not occur. The nasopharyngeal carrier state was permanently eliminated in nearly all cases.

The administration of penicillin parenterally or locally had no effect clinically or bacteriologically in two cases of extensive pyodermia. The flora of the lesions also contained a penicillin-resistant Staph. aureus hemolyticus. The streptococci themselves were inhibited by .02 unit of penicillin/cc. The concomitant presence of a potentially penicillinase-producing organism in the dermal lesions may have affected the results. Prompt cure was obtained with aureomycin ointment.

A week long course of penicillin 300,000 units/day did not sterilize the pus in an abscess of a cervical gland which was subsequently drained surgically. These were the only failures with the parenteral use of the drug. A few cases treated with local or oral therapy failed to respond but there was good evidence that the drug had not been properly administered at home.

Second Four Years of Life

A disease believed to be caused by group A hemolytic streptococci was diagnosed in 43 children from 49 to 96 months of age by methods similar to those described in the last section. Twelve clinically recognizable reinfections were also studied. Bacteriologic and immunologic evidence of recent infection by these organisms was obtained in 10 additional cases but the observed clinical illness did not appear to be streptococcal and these cases were not included in the analysis.

General Information: The attainment of the fourth year of age was associated with a striking change in streptococcal infection. There was a sharp reduction in the frequency of suppurative complications (table 2), particularly of the middle ear. This area was involved in only 9.1% of these children as contrasted with 43% of all children less than 4 years old, and 55% of those less than 2 years of age. Pyodermia was present in 27% and suppurative adenitis in 3% of these older children. One child had two episodes of suppurative vaginitis. There was not any significant difference in the frequency of complications in children from 49 to 77 months and in those from 73 to 96 months of age. Uncomplicated nasopharyngitis was diagnosed in 67% of children more than 4 years of age, but in only 17% of the younger group.

Twelve of 22 proved reinfections were studied clinically. They were not materially different from the first infections except that otitis media did not occur.

Onset and Early Symptoms: The onset of the streptococcal illness (table 3) was acute and associated with a sharp febrile response in 56% of this group of cases. There was a definite complaint of sore throat in most instances. No such dramatic events characterized the early phase of the disease in others in which there usually were either no respiratory symptoms or an initial rhinorrhea similar to that described in younger children. Definite sore throat without a febrile onset was observed in a few cases. The distribution of frequency of the two patterns of onset in children from 49 to 72 months and from 73 to 96 months of age was similar but rhinorrhea was much less, and sore throat much more common in the older group. Abdominal pain or vomiting were important early symptoms in only 14%.

First Clinic Visit and Onset of Complications: The acuity and severity of the onset of streptococcal disease in this age group led to requests for medical care early (table 4) in the course of the disease. Seventy per cent of those with respiratory symptoms were seen within the first week, and usually within the first three days of illness. The increased subjective response of these older children to illness and their augmented ability to describe their complaints doubtless contributed in part to the earlier clinic visits and to the frequency with which sore throat was noted as an initial symptom.

Suppurative complications which were associated with a definite respiratory disease also appeared early, and all were present by the end of the second week.

Physical Signs: The physical signs in 31 early cases of streptococcal respiratory infection in children more than 4 years of age are presented in table 5. Tonsillar and/or pharyngeal exudate was described in 55% and tender anterior cervical adenitis in a similar proportion of cases. A gland was fluctuant in two. Both of these signs were absent in 29%. Rhinorrhea was noted in approximately 60% of the younger, and 30% of the cases in the older groups and the nasal discharge, when examined bacteriologically, contained large numbers of group A streptococci.

Four of these cases, or approximately 10% of those in this age group with respiratory symptoms, were discovered to have a typical scarlatinaform skin rash. Temperatures greater than 37.8°C. were recorded in 42% of all cases in this age group and in 57% of those with respiratory tract disease, when they were first seen in the clinic. Twenty-seven per cent of the latter group had temperatures of 38.3°C. or more.

Laboratory: Large numbers of group A streptococci were isolated from the nasopharynx and/or the purulent discharges in all these cases. The results of the clinicolaboratory procedures are presented in table 7. Significant leucocytosis (12,000/cmm.) was discovered in approximately half the cases of nasopharyngitis studied during the first five days of illness but in only 2 of 11 with suppurative complications. The hemoglobin was less than 11 gm./100 cc. blood in only a few of these cases, reflecting the short duration of the illness, and rarely increased significantly following treatment. Anemia was present in 5 of 7 children with pyodermia. A good hematologic response followed therapy in four of these.

The erythrocyte sedimentation rate was elevated (>15 mm./hour) in two-thirds of all cases. Two-thirds of these had returned to normal within one month.

Course: Thirty-seven of the 55 infections in children from 4 to 9 years of age were treated with penicillin at varying intervals after the onset which altered the course of the disease. Eighteen were not so treated including 11 in the group from 48 to 72 months of age. Four of the latter who had had an acute febrile onset were well within 5 to 7 days.

Two similar cases had low grade fever and malaise for 10 and 14 days. One was afebrile in two days but large tender cervical glands persisted for 10 days. Two additional cases were afebrile and had rhinorrhea which persisted in association with malaise for circa 15 and 30 days before spontaneous recovery occurred. Otitis media was present in two of other untreated cases and required approximately four weeks for spontaneous resolution to occur.

Seven of the children from 72 to 96 months of age received no penicillin. Five were well in one week or less, and one had malaise without localizing symptoms or signs for 14 days. He had had a skin rash. Large, tender cervical glands and malaise, but no fever, persisted in another case for two weeks.

Hemolytic streptococci could be recovered from the nasopharynx of these untreated patients for long periods of time. These organisms had disappeared from this area in three by the third week, but persisted in all of the others throughout the period of follow-up which varied from 4 to 15 weeks.

Nonsuppurative Complications: Nonsuppurative complications were sought in these children by detailed serial study. Typical acute arthritic rheumatic fever with atrioventricular dissociation developed in a girl 52 months of age approximately 2.5 weeks after the onset of scarlet fever complicated by otitis media and suppurative cervical adenitis. Penicillin was not administered until the 10th day of illness when she first appeared at the clinic.

A boy 8 years of age had an uneventful convalescence from a streptococcal respiratory infection associated with slight fever and sore throat. A second illness, clinically similar but with severe sore throat which occurred two months later, was followed by the onset of a nonarthritic illness lasting several months which was associated with low grade fever, tachycardia, severe malaise, prolongation of the PR and QT intervals, and a persistent rapid erythrocyte sedimentation rate. A significant heart murmur did not develop but there can be no doubt that this was an example of nonarthritic rheumatic fever.

Another child, 56 months of age, developed arthralgia which persisted for a week about 30 days after a streptococcal respiratory infection. Low grade fever and leucocytosis were present for three weeks but there was no evidence of carditis. The erythrocyte sedimentation rate did not return to normal levels for more than two months.

The ECG became abnormal in three other children during convalescence from group A respiratory infections. In the case of one child, aged 61 months, the second of two studied infections was followed on the 21st day by prolongation of the PR interval which was accompanied by a rapid erythrocyte sedimentation rate but no demonstrable illness. Both laboratory abnormalities persisted for two months. Another child, aged 69 months, developed high fever, prolongation of the PR interval, and a rapid erythrocyte sedimentation rate about two weeks after a streptococcal infection. This disorder was not studied to its termination.

A respiratory infection complicated by recurrent streptococcal pyodermia in a boy 96 months of age was followed on the 30th day by the appearance of prolongation of the PR and QT intervals. These abnormalities persisted for at least one month. The erythrocyte sedimentation rate was rapid and remained so for months. The hemoglobin fell to 9.5 gm./100 cc., he failed to regain full health, and was admitted to a convalescent home, where he remained for one year before complete recovery was attained.

In addition to these 6 (10.9%) instances in which streptococcal infection in older children was followed by an apparently definite nonsuppurative complication, there were 4 cases (7.3%) in which the erythrocyte sedimentation rate was still abnormally rapid

between the 20th and 45th days. The significance of this observation cannot be assessed. Suppurative complications were not present to account for the abnormality and the children were well.

The blood pressure was recorded on each visit and at least one urine examination was obtained during the third or fourth week of follow-up in nearly all instances. No clinical or laboratory evidence of nephritis was obtained in any case. Ten type 12 infections were studied in detail over a period of one month or longer with suitable urine examinations in nine. Five received penicillin within the first week of illness and, in five, it was not used. Their ages varied from 49 to 96 months. No renal disease was discovered in any of these children.

Treatment: Detailed discussion of the penicillin treatment of hemolytic streptococcal infection in this age group is not necessary since many authors have described the great benefits to be derived from the use of this agent in older children and young adults with disease caused by these organisms. The expected rapid improvement with resolution of suppurative complications and disappearance of the streptococci from the nasopharynx was experienced. Recent interest has centered around the prevention of rheumatic fever by early and adequate treatment of streptococcal infection with penicillin. None of the six individuals in whom a definite or probable nonsuppurative complication developed was treated with this drug during the first 10 days of illness.

Relationship of Antibody Response to Nature of Clinical Disease

Three well defined patterns of antistreptolysin O response following hemolytic streptococcal infection in childhood were described in a previous paper.[3] The first (Pattern I), which was observed in infants, was characterized by a feeble production of antibody in which the maximum titer never exceeded 12 units/cc. even in the presence of suppurative complications. The response in the second (Pattern II) was moderate to vigorous but was poorly sustained and antistreptolysin levels were very low within four months. This pattern was seen in children with a mean age of 36.7 months.

A third type (Pattern III) occurred principally in older children with a mean age of 57.9 months, and consisted of a vigorous and well sustained formation of antibody.

Evidence obtained from the study of reinfection in a small group of infants suggested that these changing patterns might well be the result of conditioning of the antibody forming tissues as the result of repeated exposure to the streptococcus rather than of simple maturation. It was of considerable interest to compare the nature of streptococcal disease with the antibody pattern in the children in the study group since a similar mechanism has been proposed to explain the alterations which occur in the clinical illness with advancing age.

For this purpose 35 cases with typical infantile forms of streptococcosis as described above (indolent onset, rhinorrhea, suppurative complications) have been contrasted with 27 cases of characteristic mature disease (acute febrile onset with sore throat) in the first two columns of table 7. These cases were selected purely on the basis of adequacy of clinical observation and of serial antibody determinations.

Cases complicated by pyodermia are included separately in Column 5 since it was apparent that infection of the skin was associated with a Pattern III response much more frequently than that limited to the respiratory tract and its associated structures. This phenomenon was particularly apparent in children less than 48 months of age.

The data demonstrate a considerable correlation between antibody response and type of

TABLE 7

RELATIONSHIP OF CLINICAL DISEASE TO PATTERN OF ANTISTREPTOLYSIN RESPONSE

Age (mo.) and Antibody Pattern	Indolent Onset and Rhinorrhea With and Without Suppurative Complications*	Acute Febrile Onset with Sore Throat*	All Cases Pharyngeal Exudate	All Cases with Scarlatinaform Rash	All Cases with Pyodermia
0 to 24 mo.					
Pattern I	10	—	—	—	—
Pattern II	9	1	—	—	1
Pattern III	1	—	—	—	2
25 to 48 mo.					
Pattern I	1	—	—	—	—
Pattern II	4	2	—	—	1
Pattern III	4	1	—	—	10
49 to 72 mo.					
Pattern I	—	—	—	—	—
Pattern II	4	2	1	—	1
Pattern III	1	11	7	2	3
73 to 96 mo.					
Pattern I	—	—	—	—	—
Pattern II	—	1	—	—	—
Pattern III	1	9	6	2	4
All Ages					
Pattern I	11	—	—	—	1
Pattern II	17	6	1	—	3
Pattern III	7	21	13	4	19

* Cases without respiratory symptoms or with pyodermia excluded.

disease. Pattern I was always associated with the infantile form of streptococcal illness. A similar clinical picture was exhibited by 74% of those infections associated with Pattern II but by only 25% of those with Pattern III.

These results are vitiated by the fact that all but one of the subjects less than 24 months had the infantile, and all but one of those greater than 72 months the adult reaction to streptococcus. The results in the transitional period from 25 to 72 months are similar to those just described but it is evident that a considerable number of cases with indolent onset and rhinorrhea had Pattern III responses. The latter pattern was observed in 81% of cases with an acute febrile onset and sore throat, and the remainder exhibited Pattern II.

Pattern III was demonstrated in all but one of 14 cases with tonsillar or pharyngeal exudate and in all of four with a scarlatinaform skin rash.

Additional information in regard to this subject is presented below in a description of the sequence of events in three children who were reinfected and who are not included in the tabulation just described.

REINFECTION

Reinfection by hemolytic streptococci was recognized on 55 occasions among these children by the application of serial bacteriologic and immunologic study. Only 19 of these in 15 patients were adequately investigated clinically during the course of the new illness.

Data obtained from these cases was analyzed to determine whether any light could be cast on the possible role of reinfection in the alteration of tissue response to the streptococcus.[1, 8, 9]

The results in eight patients were not of value because the first illness was of the adult type and four were not helpful because both initial and later infections were pure pyodermias without respiratory symptoms. Three presented instructive features and will be briefly described.

Case Reports

Case 53: A 15 mo. old female was first seen during the first week of a type 12 streptococcal infection. The onset was indolent, there was no pharyngeal exudate or adenitis, and otitis media was present. Penicillin therapy was begun on the ninth day and she recovered uneventfully. The antibody response was that of Pattern I. She remained well until the 21st month when infection by a type 44 streptococcus was accompanied by a sharp febrile onset. There were no definite respiratory symptoms and the pharynx was not grossly abnormal. Leucocyte count was 33,000/cmm. Penicillin was first administered on the sixth day and was followed by rapid recovery. The antibody pattern was that of Type II.

A third infection 2 mo. later also began acutely with high fever but was complicated by otitis media. The physical examination on this occasion was different since the pharyngeal tissues were swollen and fiery red and tender anterior cervical adenitis was present. She responded well to penicillin and the antibody pattern was that of Type II. Two months later another illness, caused by a streptococcus of type 41, occurred. It was a typical, acute tonsillitis with high fever, sore throat, pharyngeal edema and redness, and tender adenitis. Exudate was not described. Otitis media was again a complication. Treatment with penicillin was effective. Pattern III antibody response was observed.

Summary.—A series of 4 group A hemolytic streptococcal infections occurred in a girl between the ages of 15 and 26 mo. The antibody response became progressively more mature with each and the illness changed from the typical indolent infantile type to that usually seen in older children. She was unusually susceptible to infection of the middle ear.

Case 54: An 8 mo. old girl was first seen late in the course of a typical infantile type of streptococcal illness associated with otitis media and pyodermia. She was effectively treated with penicillin. The antibody response was that of Pattern I. Twelve months later she suffered another infection which began with rhinorrhea and was soon complicated by the appearance of pyodermia. There was never any fever. Penicillin was administered at the end of the first week and she recovered. The subsequent antibody response was that of Pattern II.

Three months later another infection began as an acute febrile illness associated with pharyngeal edema and redness, and with tender anterior cervical adenitis. A pyodermia of the face appeared almost at once. She was treated within the 1st 2 days with penicillin and no antibody response occurred.

Summary.—Three group A streptococcal infections occurred in a girl between the 8th and 23rd months. The 1st 2 were of the typical infantile type. The third, only 3 mo. after the second, was of the adult type. A change in antibody response from that of Pattern I to that of Pattern II was noted.

Case 35: A 49 mo. old girl was first seen on the fourth day of a streptococcal respiratory infection. The onset was indolent and the first symptom was rhinorrhea followed within 2 days by the appearance of otorrhea. Large numbers of type 12 streptococci were recovered from the nasal and otitic discharges and from the nasopharynx. Penicillin was first administered on the seventh day of illness with an excellent result. The antistreptolysin response was that of Pattern I. Another infection by an untypable group A streptococcus occurred 15 mo. later when she was 64 mo. of age. It was accompanied by a sharp febrile onset, sore throat, exudative tonsillitis, and tender anterior cervical adenitis. Penicillin was first given on the second day of illness. The antibody pattern was that of Type II.

Summary.—Typical infantile streptococcal disease, associated with a Pattern I antistreptolysin response, occurred at 49 mo. of age. A second infection 15 mo. later was of the characteristic adult type and the antibody production was also of a more mature pattern.

Comment: The 1st 2 cases illustrate the changing clinical and immunologic responses to repeated hemolytic streptococcal infection in infancy. Disease of a progressively more mature type,

and more vigorous and well sustained antibody production was associated with each successive illness. The third case demonstrates that similar events may occur at a much later age. This child had an infantile clinical and immunologic reaction to streptococcus at 49 mo. of age. Another infection 15 mo. later was of the typical adult type with an intermediate antibody pattern.

Correlative Comment

A previous report demonstrated that hemolytic streptococcal infection was a commonplace among children attending the outpatient clinic of a medical school in San Francisco. More than 15% of all respiratory infections recognized clinically in this group were caused by these organisms. This could not be presumed to reflect the actual incidence of streptococcal illness in this population since older children were brought to the clinic only when disease of considerable severity was present. Large numbers of mild infections, most of which were nonbacterial, in the same subjects were not studied. It was estimated that approximately 5% of all respiratory disease might be caused by hemolytic streptococci.

In another phase of the study infants were followed serially from birth for four years. Approximately one-quarter of the previously uninfected were shown to have acquired streptococcal disease and a slightly larger proportion to have been reinfected each year. Details of the clinical aspects of this investigation are presented herein. The significant feature was the fact that less than one-fifth of the streptococcal infections recognized by bacteriologic and immunologic methods were sufficiently severe to require medical care. Children less than 30 months of age were brought to the clinic only when a suppurative complication had supervened. Such extension of infection developed in only 7.7% of streptococcal infections in the whole group and in only 9% of those in infants under 30 months of age. Definitive medical care was required in a much greater number of nonstreptococcal respiratory infections during the four year period. Otitis media caused by other organisms was three times as frequent as that caused by streptococci.

These observations demonstrated that hemolytic streptococcal infection was a frequent event during the first four years of life among these children but that it was usually mild or inapparent and infrequently associated with suppurative complications. Nonstreptococcal disease was a more important therapeutic problem.

The remainder of the report is concerned with the definition of the nature of infection by group A hemolytic streptococci in children of various ages as determined by the study of established disease discovered by the application of clinical, bacteriologic and immunologic methods in children with respiratory illness who were attending the clinic.

Streptococcal disease during the first four years of life was marked by the absence of an acute onset and by a subacute protracted course. Rhinorrhea was the earliest symptom in most cases and presumably accompanied a streptococcal sinusitis. Fever was rarely recognized in the absence of a complication. The children had usually been ill for days to weeks when they were first brought to the clinic. This action was usually dictated by the appearance of a suppurative complication, most often otitis media or pyodermia. Not infrequently one of these complications developed in the absence of any respiratory symptoms in children believed to be well. In such cases large numbers of hemolytic streptococci were always present in the nasopharynx as well as in the purulent discharges.

When these young children were examined tonsillar and pharyngeal exudate was never described and tender anterior cervical adenitis was only occasionally present. Nasal discharge was present in three-quarters of the cases but was not always recognized at the time of examination as purulent or likely to be the result of streptococcal infection. Accurate

clinical diagnosis was impossible in this age group and the etiologic agent was often suspected only after the results of cultural studies of material from the nasopharynx or of the purulent discharges. The concatenation of a respiratory infection with rhinorrhea and an impetiginous skin lesion should strongly suggest the diagnosis of streptococcal disease.

Significant leucocytosis (>12,000 cells/cmm.) was present in about half the small group of cases without otitis media, suppurative adenitis, or pyodermia. This laboratory procedure, when an abnormal value is obtained, would seem to be of value in distinguishing streptococcal and nonstreptococcal respiratory infection in these young children as it may be in older children and adults in the absence of a suppurative complication such as otitis media. The presence of the latter, regardless of the bacterial etiology, will be associated with leucocytosis in many cases.

The erythrocyte sedimentation rate was nearly always rapid except in instances where pyodermia was the predominant manifestation of the disease. This test is, of course, of no value in differential etiologic diagnosis.

This study did not permit an accurate definition of the course and natural history of group A streptococcal infection in young children since only a few were seen near the onset and without a suppurative complication. The previously described serial study demonstrated that these serious extensions of the disease process were rare manifestations of streptococcal infection in children less than four years of age. It was evident that many of the children had suffered a debilitating subacute illness prior to the onset of the complication. Significant anemia was present in many, including those without a complication, and excellent hematologic response occurred after effective antimicrobial therapy was instituted.

The etiology of such illnesses must usually be overlooked in medical practice and a considerable disability among children may result. This is particularly unfortunate since the results of penicillin therapy were exceedingly satisfactory and were associated with the rapid disappearance of hemolytic streptococci from the nasopharynx and the purulent discharges, and with striking clinical improvement. The latter was often evident within 48 hours and was sustained if effective therapy was continued for about one week. Previous experience indicated that short courses of penicillin (72 hours or less) would have been associated with frequent bacteriologic and clinical relapse.

None of the infections in children less than 4 years of age was accompanied by a skin rash nor was any followed by a nonsuppurative complication such as rheumatic fever or glomerulonephritis. Particularly noteworthy was the complete absence of even minor evidence of rheumatic activity such as late fever or abnormalities of the ECG during convalescence.

The forty-eighth month marked a change in the clinical manifestations of streptococcal respiratory infection. During the fifth and sixth years the infantile form of the disease was seen quite frequently and otitis media, suppurative lymphadenitis, and pyodermia occurred in many of these cases.

Most striking was the appearance of an illness characterized by an acute febrile onset, sore throat and exudative tonsillitis. Rhinorrhea was much less common in these individuals and suppurative complications were rare. During the seventh and eighth years this form of the disease was almost the only type seen. A scarlatinaform skin rash was observed in a few of these children more than 4 years of age. The response of these infections to

penicillin therapy was excellent but not so dramatic as in the younger age groups since streptococcal disease of the adult type is essentially self limited and suppurative complications are much less common.

Particularly interesting was the appearance of definite rheumatic fever, of late fever, and of abnormalities of the ECG during convalescence in this age group since all of these certain or probable manifestations of the rheumatic state were completely absent in younger children.

The pathogenesis of these changing patterns of response to the hemolytic streptococcus is of the greatest interest. It has previously been proposed that they are the result of alterations in the reaction of the tissues as a result of repeated exposure to the streptococcus.[1, 8, 9] Some evidence in support of this hypothesis was obtained by the study of two cases in which repeated infection by these organisms occurred during infancy. In both the infantile form was replaced by progressively more adult disease with every illness, and by a shift in the antibody response to a more mature pattern. The last infection in each at less than 30 months of age was quite like that observed in older children and uncommonly seen in such young babies.

A similar sequence of events occurred in another child 4 years of age demonstrating that simple maturation of tissues may not be responsible for the phenomenon under discussion. A correlation was demonstrated between the type of antistreptolysin O response and the nature of the clinical illness. It was not sufficiently exact to permit definitive conclusions as to pathogenesis of changing tissue reaction to the streptococcus even though it were proved that the alterations in antibody pattern were the result of reinfection by hemolytic streptococci.[8] This hypothesis is reasonable but is not established.

The evidence obtained during this investigation offers some support to the point of view that the differences between children of various ages in their response to group A hemolytic streptococci are the result of serial reinfection, presumably by strains of different serologic type, and that the alterations in reaction may be the result of immunologic processes. It is doubtful that any study in human beings can finally settle this matter because far too many uncontrolled variables are at work.

Summary

This report describes a study of hemolytic streptococcal infection during the first eight years of life. Serial study of a group of babies from birth through the fourth year demonstrated that infection by the hemolytic streptococcus was a frequent event but that the disease was usually mild or inapparent.

Hemolytic streptococcal infection during the first four years of life in its more severe form was characterized by the lack of an acute onset, by low grade or absent fever, by rhinorrhea, by a protracted un-self limited course, and by the occurrence of frequent suppurative complications.

Accurate etiologic diagnosis in these cases required bacteriologic study of the nasopharyngeal flora and of the purulent discharges. The administration of penicillin abruptly terminated the disease process in these cases with prompt and dramatic clinical improvement.

After the fourth year the disease pattern changed so that progressively more of the infections were associated with an acute febrile onset, sore throat, exudative tonsillitis and pharyngitis, and occasionally with a skin rash.

Rheumatic fever and lesser manifestations of the rheumatic state occurred following

streptococcal infection in children more than 4 years of age but were never observed in younger ones.

Evidence is presented which supports but does not establish the validity of the hypothesis that the changing patterns of clinical response to hemolytic streptococci are the result of repeated infection by these organisms with an alteration in tissue reactivity presumably on an immunologic basis.

References

1. Powers, G. F., and Boisvert, P. L., Age as factor in streptococcosis, J. Pediat. **25**:481, 1944.
2. Rantz, L. A., Maroney, Margaret, and Di Caprio, J. M., Infection and reinfection by hemolytic streptococci in early childhood, in Rheumatic Fever: Symposium, Minneapolis, University of Minnesota Press, 1952.
3. Rantz, L. A., Maroney, Margaret, and Di Caprio, J. M., Antistreptolysin O response following hemolytic streptococcus infection in early childhood, Arch. Int. Med. **87**:360, 1951.
4. Di Caprio, J. M., Rantz, L. A., and Randall, E., Studies on streptococcal hyaluronidase and anti-hyaluronidase, Arch. Int. Med. **89**:374, 1952.
5. Pike, R. M., and Fashena, G. J., Frequency of hemolytic streptococci in throats of well children in Dallas, Am. J. Pub. Health **36**:611, 1946.
6. Swift, H. F., Wilson, A. T., and Lancefield, R. C., Typing group A hemolytic streptococci by M precipitin reactions in capillary pipettes, J. Exper. Med. **78**:127, 1943.
7. Rantz, L. A., and Randall, E., Modification of technique for determination of antistreptolysin titer, Proc. Soc. Exper. Biol. & Med. **59**:22, 1945.
8. Rantz, L. A., Boisvert, P. L., and Spink, W. W., Etiology and pathogenesis of rheumatic fever, Arch. Int. Med. **76**:131, 1945.
9. Murphy, G. E., and Swift, H. F., Induction of cardiac lesions, closely resembling those of rheumatic fever, in rabbits following repeated skin infections with Group A streptococci, J. Exper. Med. **89**:687, 1949.

Spanish Abstract

Infecciones por Estreptococo Hemolítico en la Infancia

El presente trabajo trata de un estudio sobre las infecciones por estreptococo hemolítico durante los primeros años de la vida. Los autores llegan a la conclusión de que la infección de este tipo es muy frecuente desde el nacimiento hasta el cuarto año de edad, pero con manifestaciones generalmente benignas e inaparentes; al presentarse en forma más severa, las características observadas fueron: Principio insidioso con febrícula o ausencia de fiebre, rinorrea, curso prolongado sin autolimitación y complicaciones supurativas frecuentes. El diagnóstico etiológico exacto requiere estudio bacteriológico tanto de la flora nasofaríngea como de las secreciones purulentas. La terapéutica con penicilina termina en forma rápida el proceso patológico, observándose en ocasiones una mejoría clínica dramática.

Por el contrario, después del cuarto año de edad, la infección estreptocóccica presenta un patrón diferente: el proceso se inicia con un cuadro febril agudo, dolor faríngeo, amigdalitis exudativa, faringitis y en ocasiones erupción en la piel. Se observa fiebre reumática o bien manifestaciones más ligeras de proceso reumático en los niños mayores de cuatro años, contrastando con su ausencia en niños menores de esa edad.

Los autores consideran que la diversidad de los cuadros clínicos como respuesta al estreptococo hemolítico es el resultado de repetidas infecciones que provocan alteraciones de la reacción tisular desde el punto de vista de su base inmunológica.

Stanford University School of Medicine

LYMPHOID HYPERPLASIA OF THE APPENDIX

Clinical Study

By ALFRED A. NATHANS, M.D., HYMAN MERENSTEIN, M.D., AND SAMUEL S. BROWN, M.D.
Brooklyn

ALTHOUGH lymphoid hyperplasia of the appendix is a frequently encountered pediatric entity, the standard texts and the literature treat with it sparsely and emphasize principally its role in the pathogenesis of acute appendicitis. The condition, once diagnosed, is often entertained as a benign disturbance, transient in character with subsequent return of the appendix to its normal state. This misconception on the part of the physician, with his associated sense of complacency once the diagnosis of lymphoid hyperplasia of the appendix is made, is to be brought to his attention. Bohrod[1] quotes the late Dr. Brennemann as having regretted describing this syndrome "since there were times when clinicians having made that diagnosis, neglected to watch for the development of a true infective appendicitis."

The purpose of this paper is to focus attention on the existence of this condition, to point out that it is not always a benign self-limiting disease, and to describe its clinical features.

METHOD

This study consists of an analysis of the clinical history, the physical findings, and the histologic examination of the removed appendix in 198 cases in which a microscopic diagnosis of lymphoid hyperplasia of the appendix was made either as the sole diagnosis or in those cases where lymphoid hyperplasia represented an appreciable part of the microscopic picture. The pathologic diagnosis was based on the presence of many large lymphoid follicles with large active germinal centers (see Fig. 3).

FINDINGS

In 196 of these cases a preoperative diagnosis of acute appendicitis had been made. One case, an ectopic pregnancy, had coincidental removal of the appendix. Another appendix was removed during

TABLE 1

AGE DISTRIBUTION

Birth to 5 yr.	5+ to 10 yr.	10+ to 15 yr.	15+ to 20 yr.	20+ to 25 yr.	25+ to 30 yr.	30+ to 35 yr.	35+ to 40 yr.	40+ to 45 yr.	45+ to 50 yr.	50+ to 55 yr.	55+ to 60 yr.	60+ to 65 yr.	65+ to 70 yr.
36 (18.2%)	84 (42.4%)	43 (21.2%)	14 (7.1%)	8 (4.1%)	3 (1.5%)	3 (1.5%)	4 (2%)	2 (1%)	0	0	0	0	1 (0.5%)

a herniorrhaphy because of its presence in the hernial sac. There were 97 males and 101 females. The youngest patient was 28 mo. and the oldest 68 yr. The average age was 11.3 yr. The age distribution is indicated in table 1.

Initial Symptoms: In 177 (89.4%) of the patients the initial symptom was pain alone. Pain accompanied by vomiting, as an initial symptom, was present in 8 cases and pain associated with

From the Departments of Pediatrics and Pathology, The Jewish Hospital of Brooklyn, Brooklyn.
(Received for publication April 27, 1953.)

TABLE 2

SPASM

None	1+	2+	3+	4+
119 (60.1%)	54 (27.3%)	17 (8.6%)	5 (2.5%)	3 (1.5%)

TABLE 3

RIGIDITY

None	1+	2+	3+	4+
178 (89.9%)	7 (3.5%)	7 (3.5%)	4 (2%)	2 (1%)

nausea and vomiting occurred in one case. In only 10 cases was pain absent initially. In this group there were 6 cases of initial vomiting and nausea, 2 cases of nausea and one of vomiting. The only symptomless patient had the appendix removed during a herniorrhaphy.

Character of the Pain: In 161 of the cases (81.3%) the pain was noncolicky. Thirty-six had colicky pain. In 25 patients the pain was severe, and in 172 the pain was slight to moderate.

Incidence of Other Symptoms: Nausea occurred in 130 (66%) of the patients and vomiting in 105 (53%). Fifteen had diarrhea and 5 were constipated. Previous similar attacks occurred in 26 cases (13%).

Tenderness: Direct abdominal tenderness of varying degree characterized all of the cases except the one previously mentioned. In 185 (92.4%) there was tenderness in the right lower quadrant, and in 12 cases the tenderness was generalized. Fifty-three patients (26.7%) had rebound tenderness. The tenderness was severe in 8 instances and mild to moderate in 179.

Spasm and Rigidity: The frequency of spasm and rigidity and their relative degree is indicated in tables 2 and 3.

TABLE 4

ADMISSION TEMPERATURES

37.0° C. or less	37.0°+ to 37.8°	37.8°+ to 38.3°	38.3°+ to 38.9°	38.9°+ to 39.4°	39.4°+ to 40.0°
16	71	56	28	10	17

TABLE 5

TOTAL WHITE COUNTS

White Count	No. of Cases
Below 6,000	9
6,000 to 9,000	54
9,000 to 12,000	33
12,000 to 15,000	46
15,000 to 18,000	22
18,000 to 21,000	21
21,000 to 23,000	7
Above 23,000	13

TABLE 6

POLYMORPHONUCLEAR COUNTS

Poly. Counts	No. of Cases
20% to 30%	1
30% to 40%	5
40% to 50%	1
50% to 60%	14
60% to 70%	41
70% to 80%	57
80% to 90%	46
90% to 100%	20

TABLE 7

LYMPHOCYTE COUNTS

Lymph. Counts	No. of Cases
0 to 10%	26
10% to 20%	50
20% to 30%	56
30% to 40%	30
40% to 50%	9
50% to 60%	3
60% to 70%	1
70% to 80%	1
80% to 90%	0
90% to 100%	0

LYMPHOID HYPERPLASIA OF THE APPENDIX

Clinical Study

By ALFRED A. NATHANS, M.D., HYMAN MERENSTEIN, M.D., AND SAMUEL S. BROWN, M.D.
Brooklyn

ALTHOUGH lymphoid hyperplasia of the appendix is a frequently encountered pediatric entity, the standard texts and the literature treat with it sparsely and emphasize principally its role in the pathogenesis of acute appendicitis. The condition, once diagnosed, is often entertained as a benign disturbance, transient in character with subsequent return of the appendix to its normal state. This misconception on the part of the physician, with his associated sense of complacency once the diagnosis of lymphoid hyperplasia of the appendix is made, is to be brought to his attention. Bohrod[1] quotes the late Dr. Brennemann as having regretted describing this syndrome "since there were times when clinicians having made that diagnosis, neglected to watch for the development of a true infective appendicitis."

The purpose of this paper is to focus attention on the existence of this condition, to point out that it is not always a benign self-limiting disease, and to describe its clinical features.

METHOD

This study consists of an analysis of the clinical history, the physical findings, and the histologic examination of the removed appendix in 198 cases in which a microscopic diagnosis of lymphoid hyperplasia of the appendix was made either as the sole diagnosis or in those cases where lymphoid hyperplasia represented an appreciable part of the microscopic picture. The pathologic diagnosis was based on the presence of many large lymphoid follicles with large active germinal centers (see Fig. 3).

FINDINGS

In 196 of these cases a preoperative diagnosis of acute appendicitis had been made. One case, an ectopic pregnancy, had coincidental removal of the appendix. Another appendix was removed during

TABLE 1

AGE DISTRIBUTION

Birth to 5 yr.	5+ to 10 yr.	10+ to 15 yr.	15+ to 20 yr.	20+ to 25 yr.	25+ to 30 yr.	30+ to 35 yr.	35+ to 40 yr.	40+ to 45 yr.	45+ to 50 yr.	50+ to 55 yr.	55+ to 60 yr.	60+ to 65 yr.	65+ to 70 yr.
36 (18.2%)	84 (42.4%)	43 (21.2%)	14 (7.1%)	8 (4.1%)	3 (1.5%)	3 (1.5%)	4 (2%)	2 (1%)	0	0	0	0	1 (0.5%)

a herniorrhaphy because of its presence in the hernial sac. There were 97 males and 101 females. The youngest patient was 28 mo. and the oldest 68 yr. The average age was 11.3 yr. The age distribution is indicated in table 1.

Initial Symptoms: In 177 (89.4%) of the patients the initial symptom was pain alone. Pain accompanied by vomiting, as an initial symptom, was present in 8 cases and pain associated with

From the Departments of Pediatrics and Pathology, The Jewish Hospital of Brooklyn, Brooklyn.
(Received for publication April 27, 1953.)

TABLE 2

SPASM

None	1+	2+	3+	4+
119 (60.1%)	54 (27.3%)	17 (8.6%)	5 (2.5%)	3 (1.5%)

TABLE 3

RIGIDITY

None	1+	2+	3+	4+
178 (89.9%)	7 (3.5%)	7 (3.5%)	4 (2%)	2 (1%)

nausea and vomiting occurred in one case. In only 10 cases was pain absent initially. In this group there were 6 cases of initial vomiting and nausea, 2 cases of nausea and one of vomiting. The only symptomless patient had the appendix removed during a herniorrhaphy.

Character of the Pain: In 161 of the cases (81.3%) the pain was noncolicky. Thirty-six had colicky pain. In 25 patients the pain was severe, and in 172 the pain was slight to moderate.

Incidence of Other Symptoms: Nausea occurred in 130 (66%) of the patients and vomiting in 105 (53%). Fifteen had diarrhea and 5 were constipated. Previous similar attacks occurred in 26 cases (13%).

Tenderness: Direct abdominal tenderness of varying degree characterized all of the cases except the one previously mentioned. In 185 (92.4%) there was tenderness in the right lower quadrant, and in 12 cases the tenderness was generalized. Fifty-three patients (26.7%) had rebound tenderness. The tenderness was severe in 8 instances and mild to moderate in 179.

Spasm and Rigidity: The frequency of spasm and rigidity and their relative degree is indicated in tables 2 and 3.

TABLE 4

ADMISSION TEMPERATURES

37.0° C. or less	37.0°+ to 37.8°	37.8°+ to 38.3°	38.3°+ to 38.9°	38.9°+ to 39.4°	39.4°+ to 40.0°
16	71	56	28	10	17

TABLE 5

TOTAL WHITE COUNTS

White Count	No. of Cases
Below 6,000	9
6,000 to 9,000	54
9,000 to 12,000	33
12,000 to 15,000	46
15,000 to 18,000	22
18,000 to 21,000	21
21,000 to 23,000	7
Above 23,000	13

TABLE 6

POLYMORPHONUCLEAR COUNTS

Poly. Counts	No. of Cases
20% to 30%	1
30% to 40%	5
40% to 50%	1
50% to 60%	14
60% to 70%	41
70% to 80%	57
80% to 90%	46
90% to 100%	20

TABLE 7

LYMPHOCYTE COUNTS

Lymph. Counts	No. of Cases
0 to 10%	26
10% to 20%	50
20% to 30%	56
30% to 40%	30
40% to 50%	9
50% to 60%	3
60% to 70%	1
70% to 80%	1
80% to 90%	0
90% to 100%	0

Rectal Examinations: In 170 of the patients rectal examination was either not done or was not charted. Twenty-three patients exhibited tenderness to the examining finger on the right side, 2 were tender anteriorly, and 3 were tender on both right and left sides.

Signs of Upper Respiratory Infection: Fifty (25%) of the patients had evidence of upper respiratory infection. These signs were for the most part reddening of the nasal and pharyngeal mucosae.

Temperature on Admission: The distribution of the admission temperature is shown in table 4. The average admission temperature was 38.0°C.

White Blood Cell Counts: In 13 cases the leucocyte counts were uncharted. The lowest count was 3,750 and the highest 35,000. The distribution is indicated in table 5.

Polymorphonuclear and Lymphocytic Leucocytes: The lowest polymorphonuclear count was 26% and the highest 100%. The distribution of these cell counts is shown in table 6. The distribution of the lymphocyte counts is shown in table 7.

Sedimentation Rates: Unfortunately, sedimentation rates were performed in only 13 cases. Two were normal and 11 were elevated.

Pathologic Diagnosis: In 158 (80%) of the cases lymphoid hyperplasia was present as the sole lesion. In the remainder, this condition was associated with or was the cause of a variety of other pathologic conditions. These are listed as follows:

Pathology	No. of Cases
Enlarged Mesenteric Nodes	76
Lymphoid Hyperplasia and Acute Appendicitis	21
Lymphoid Hyperplasia and Acute Suppurative Appendicitis	5
Lymphoid Hyperplasia plus Peri-appendicitis	4
Lymphoid Hyperplasia and Subacute Appendicitis	2
Lymphoid Hyperplasia and Acute Appendicitis with Fecolith	2
Lymphoid Hyperplasia and Gangrenous Appendix with Perforation	1
Lymphoid Hyperplasia and Acute Suppurative Gangrenous Appendix	1
Lymphoid Hyperplasia and Oxyuris	2
Lymphoid Hyperplasia and Ovarian Teratoma	1
Lymphoid Hyperplasia and Parovarian Cyst	1

Discussion

The amount of lymphoid tissue in the appendix varies with age. Hwang and Krumbhaar[2] studied the appendices in 300 cases of violent death at different ages. They found that the percentage of lymphoid tissue and its absolute weight are greatest in the first decade of life and thereafter diminishes steadily with advancing age.

In this series of 198 cases of lymphoid hyperplasia 60.6% occurred in the first decade of life. This indicates that the propensity for development of appendiceal symptoms due to lymphoid hyperplasia is greatest during the time when the amount of appendiceal lymphoid tissue is at its maximum. In earlier studies on the pathogenesis of acute appendicitis various authors tried to implicate lymphoid hyperplasia as an important etiologic factor. They were, however, unable to reconcile the fact that lymphoid hyperplasia was at its maximum in the first decade of life, while the greatest incidence of acute appendicitis occurred in the second decade. This paradox was resolved by Bohrod[1] by anatomic study of the appendix. The appendix of the newborn is almost devoid of lymphoid tissue (see Fig. 1). As the child grows the lymphoid tissue increases progressively until at about puberty (see Fig. 2). At this time the muscularis increases in thickness to a considerable degree causing the lumen of the appendix to become appreciably narrowed. With narrowing of the lumen, a relatively slight swelling of the lymphoid tissue is

enough to obliterate the lumen and the train of events leading to acute appendicitis is initiated (see Fig. 4).

The lability of the lymphatic system and its ready response to a wide variety of stimuli, especially infection, is well known. Abdominal symptoms suggestive of and frequently indistinguishable from acute appendicitis occur in association with upper respiratory infections.[3,4] Varicella, oxyuriasis and perhaps a high fat diet may evoke a lymphoid response in the appendix. Of considerable clinical interest is the appendiceal syndrome in preeruptive rubeola. The removed appendix in addition to the lymphoid hyperplasia exhibits the Warthin-Finkeldey cell that enables the pathologist to predict the occurrence of

FIG. 1. Appendix of newborn infant (×16). Note thinness of wall and almost complete absence of lymph follicles. Lumen is relatively wide.

rubeola.[5] In 1950 Raftery, Trafas and McClure[6] reported a 5% incidence of Histoplasma capsulatum in an unselected series of 2,135 cases in which appendectomy had been performed. In their series, 30 cases of mesenteric adenitis were reported to have had a 43% incidence of histoplasmosis. In the present authors' series it was not possible to identify any structures resembling Histoplasma capsulatum on the routine hematoxylin and eosin stained section. A recent study[7] of 100 appendices employing special staining and special cultural technics failed to show any Histoplasma capsulatum in any of the appendices, although these cases occurred in a presumably endemic area. Further study of 1,307 appendices stained with hematoxylin and eosin were negative for this organism.

The clinical picture of lymphoid hyperplasia of the appendix is one which is hardly distinguishable from that of acute appendicitis. The patient is usually a child below the age of 15 years. Abdominal pain of varying degree is generally the first complaint. This is soon followed by nausea and vomiting. The temperature is usually below 38.1°C. The white cell count may or may not be elevated and a polynucleosis may or may not occur.

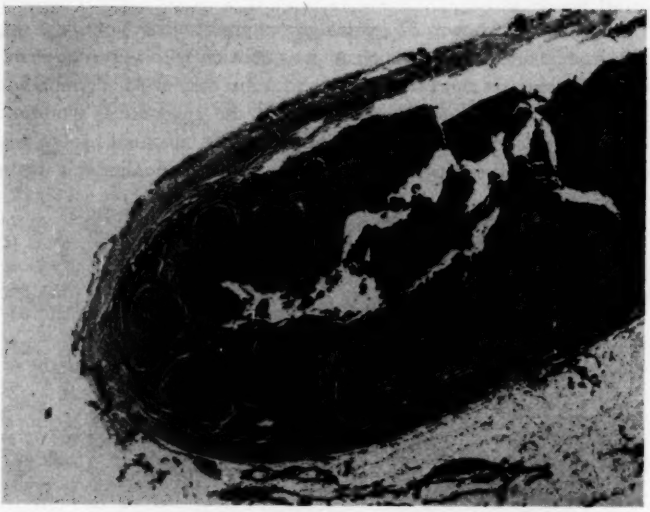


FIG. 3. Lymphoid hyperplasia in 10 yr. old girl (×16). Note large number of lymph follicles with large active germinal centers and narrow rim of lymphocytes. Lumen is narrow.

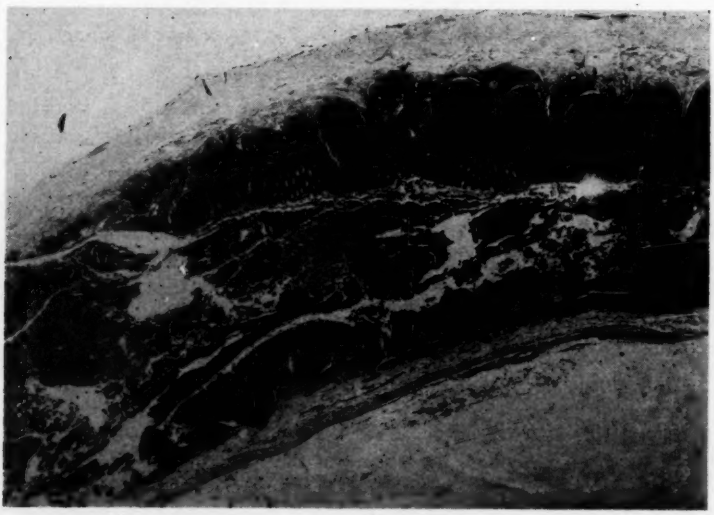


FIG. 2. Appendix in 13 yr. old girl (×16). Note abundance of lymph follicles. Wall is well represented and lumen is relatively narrow.

Varying degrees of tenderness, most often in the right lower quadrant, may be elicited. Rigidity is mostly not present, but some degree of spasm of the right rectus muscle may be elicited. In this study 40% of the patients were noted to have spasm. The authors feel that spasm is present much more frequently, and often can only be detected when comparing the difference in resistance of the right and left rectus muscles on very superficial palpation. Somewhat deeper palpation will also elicit some tenderness on the right side.

In an attempt to evaluate the significance of the data in arriving at a differential diagnosis between lymphoid hyperplasia of the appendix and acute appendicitis the authors have compared these cases with Norris'[8] series of 1,000 cases of acute appendicitis in children.

	Lymphoid Hyperplasia	Acute Appendicitis
Pain	89%	95%
Nausea	66%	85%
Right Lower Quadrant Tenderness	92%	99%
Spasm	46%	Not reported
Rigidity	10%	68%
Rebound	22%	22%
Av. Temperature	38.0°C.	38.3°C.
WBC	3,700 to 35,000 (Av. 12,900)	3,100 to 60,000 (Av. 16,700)
Polys.	74% (av.)	Not reported

In both series pain is an outstanding complaint. Nausea is common to both. Right lower quadrant tenderness is present in over 90% of the cases in each series. Rigidity is much less prevalent in lymphoid hyperplasia (10%) as compared to acute appendicitis (68%), but it is obvious that this cannot be used as a differentiating factor in the

FIG. 4. Lymphoid hyperplasia and acute appendicitis (×16). Microscopic features are similar to those in Fig. 3. Inflammatory reaction is seen on higher magnification in Figs. 5 and 6.

FIG. 5. Lymphoid hyperplasia and acute appendicitis (×200). Note diffuse cellular infiltration in wall of appendix.

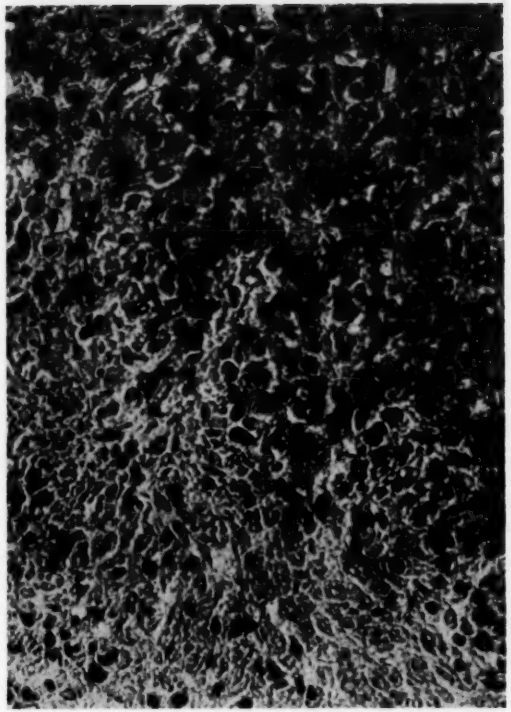


FIG. 6. Lymphoid hyperplasia and acute appendicitis (×333). Under higher magnification cellular infiltrate present in Fig. 5 is seen to be composed chiefly of polymorphonuclear leucocytes.

individual case. The presence or absence of a leucocytosis or polynucleosis is also of little help. The frequency with which a lymphoid hyperplasia progresses to an acute appendicitis, 18% in this series, tends to further complicate the picture. Although there is no certain way in which to differentiate lymphoid hyperplasia of the appendix from acute appendicitis, in the authors' experience, careful observation of the patient every 6 to 12 hours has been helpful in avoiding operation in many cases and also in bringing to earlier surgery those cases which have developed an acute appendicitis. Perhaps the most important indication for operation is any increase in the local signs, such as spasm or tenderness.

Summary

One hundred ninety-eight cases of lymphoid hyperplasia of the appendix, some of which had other associated pathology, have been analyzed.

Comparison has been made with an analogous series of acute appendicitis in children.

There is no precise differential diagnosis between acute appendicitis and lymphoid hyperplasia of the appendix. Each case has to be watched carefully, and any increase in local signs is an indication for surgery.

Lymphoid hyperplasia is frequently the precursor of acute appendicitis.

References

1. Bohrod, M. G., Pathogenesis of acute appendicitis, Am. J. Clin. Path. **16**:752, 1946.
2. Hwang, J. M. S., and Krumbhaar, E. B., Amount of lymphoid tissue of human appendix and its weight at different age periods, Am. J. M. Sc. **199**:75, 1940.
3. Brennemann, J., Abdominal pain in throat infections in children and appendicitis, J.A.M.A. **89**:2183, 1927.
4. Lowenstein, P., Respiratory diseases that mimic appendicitis, J. Missouri M. A. **29**:563, 1932.
5. Simon, M. A., and Ballon, H. C., Appendiceal lesions in prodromal stage of measles, J. Clin. Path. **18**:796, 1948.
6. Raftery, A., Trafas, P. C., and McClure, R. D., Histoplasmosis: Common cause of appendicitis and mesenteric adenitis, Ann. Surg. **132**:720, 1950.
7. Christopherson, W. M., Miller, M. P., and Kotcher, E., Examination of human appendixes for histoplasma capsulatum, J.A.M.A. **149**:1648, 1952.
8. Norris, W. J., Appendicitis in children, West. J. Surg. **54**:183, 1946.

Spanish Abstract

Hiperplasia Linfoide del Apéndice: Estudio Clínico

A pesar de la frecuencia de la hiperplasia linfoide del apéndice como entidad pediátrica, la literatura médica trata ocasionalmente y principalmente por su papel en la patogenia de la apendicitis aguda, considerándola como un trastorno benigno y transitorio con regresión pronto del apéndice a su normalidad y el paciente a su estado previo de salud. Este artículo trata de analizar dicho estado hiperplásico linfoide, recalcar que no siempre es benigno y señalar sus características clínicas basándose en 198 casos con diagnóstico o bien único de hiperplasia linfoide o bien con presencia predominante de folículos linfoideos con centros germinales activos, en el apéndice.

En 196 de estos casos se había hecho el diagnóstico pre operatorio de apendicitis aguda; en otro caso el apéndice se operó por embarazo ectópico y en el último durante una hernioplastía. 97 fueron hombres y 101 mujeres; la edad promedio fué de 11.3 años, siendo el paciente más joven de 28 meses y el más viejo de 68 años de edad. Las manifestaciones clínicas se iniciaron con dolor abdominal, ó náuseas, ó vómitos, hiperestesia cutánea y profunda, defensa muscular, fiebre, infección de vías respiratorias altas, todos o en parte presentes en grado variable de frecuencia e intensidad; los datos de laboratorio también fueron variables.

En la series de 198 casos de hiperplasia linfoide, el 60.6% se presentó en la primera década de

la vida, lo que indica la propensión de síntomas apendiculares debidos a hiperplasia linfoide en edades en que la cantidad de tejido linfoideo apendicular es mayor. El cuadro clínico de la hiperplasia linfoide del apéndice es difícil de diferenciar de la apendicitis aguda; el dolor, signo predominante, las náuseas y la hiperestesia de la fosa iliaca derecha son comunes a ambos; los demás signos y síntomas no inclinan a uno u otro diagnóstico por lo que los autores recomiendan la observación cuidadosa del paciente cada 6 o 12 horas a fin de evitar operaciones innecesarias ó realizar éstas máas tempranamente si así conviene, en particular cuando hay un aumento en la intensidad de las manifestaciones locales. Para ellos la hiperplasia linfoide es con frecuencia el antecedente de la apendicitis aguda.

555 *Prospect Place*

CONGENITAL MALFORMATIONS AND BIRTH INJURIES IN NEW YORK CITY

By HELEN M. WALLACE, M.D., LEONA BAUMGARTNER, M.D., AND HERBERT RICH
New York City

THE purposes of reporting data to an official health agency are twofold: (1) To determine the size of a particular health problem and so in part to plan enough community facilities of good quality for patient care; (2) To serve as a tool for finding the individual patient with a health problem, and for providing the necessary follow-up and care if indicated. Crippled children's programs throughout the country have for a period of years attempted to encourage reporting of certain handicapping conditions, usually on a voluntary and not a mandatory basis. It is generally accepted that such reporting is incomplete. Whether making such reporting mandatory would significantly add to the completeness is unknown. No appreciable increase in the number of known cerebral palsy cases followed mandatory reporting in one community. But it may be that adequate professional education and publicity did not accompany this effort.

Related to this problem of reporting is the question of the value of maintaining a register of reported cases. If maintained, the register should be able to serve the same two purposes mentioned above—namely, estimation of the size of the problem and follow-up of individuals reported. A register serving both of these functions is expensive to maintain. It is probable that there are other devices which will accomplish the same purposes. Special mortality and morbidity studies can be used to estimate the incidence and prevalence of the problem. Professional education and formulation of sound procedures can help to assure good case-finding and follow-up through the medical societies. hospitals and child health conferences, school health services, day nurseries, children's institutions, etc.

The confidential medical material accompanying live birth certificates is another source used in case finding. Several reports have appeared in the literature on the use of the supplemental portion of the certificate containing confidential information. The report from upstate New York (exclusive of New York City) for the period 1940-1942[1] analyzed the birth injuries and congenital malformations reported, mortality in the group reported, and correlated these findings with other methods of reporting orthopedic deformities. The second report[2] also from upstate New York considered the accuracy of reporting of birth injuries and congenital malformations via live birth certificates and showed by a sample checking with hospital records that only 34% were reported on the certificates. Similar data on birth injuries on the live birth certificate have been studied in New York City[3] and have shown over-reporting—that is, 7% of the babies reported via the live birth certificates to have birth injuries were reported by the hospitals that no evidence of such birth injuries was found during the later neonatal hospital course; under-reporting was not tested in this study.

From the Bureau for Handicapped Children, New York City Department of Health, New York City.

(Received for publication May 9, 1953.)

In New York City questions regarding the presence of birth injury or congenital malformation were introduced on the live birth certificate in 1948. Because of the paucity of such reports in the literature, further consideration of the value of the reporting of birth injuries and congenital malformations on live birth certificates in New York City is herewith presented.

Congenital Malformations

In 1951, a total of 1,501 children was reported to have been born alive with one or more congenital malformations, an over-all reported incidence of 9.2 per 1,000 live births. Table 1 shows the incidence in broad groups by systems. In the allocation of groups, certain priorities were used. If a baby had more than one malformation, the more serious condition was made the primary one, and the case so classified. The one exception

TABLE 1

Congenital Malformations by System—Incidence and Neonatal Mortality
New York City—1951

System	No. Reported	Incidence/1,000 Live Births	Neonatal Deaths	Neonatal Mortality Per Cent
Extremities	660	4.06	44	6.7
Central nervous system	227	1.39	84	37.0
Genitourinary	152	0.93	8	5.3
Cleft palate or harelip	128	0.79	15	11.7
Skin	87	0.53	3	3.4
Gastrointestinal tract	79	0.49	18	22.8
Eye, ear and nose	43	0.26	5	11.6
Heart	34	0.21	13	38.2
Neck and chest	21	0.13	5	23.8
Other bone malformations	18	0.11	3	16.7
Miscellaneous	52	0.32	20	38.5
Total	1,501	9.22	218	14.5

to this rule was cleft palate or harelip which was given a primary priority also. Malformations with the greatest reported frequency occurred in the extremities, central nervous system and genitourinary system. A further analysis shows that the most frequent types of reported congenital malformations are club foot, the various types of dactylism, cleft palate and harelip, hypospadias and spina bifida (table 2).

A comparison of these 1951 New York City data with the upstate New York data of 1940-1942 reveals considerable similarity of reported incidence. The over-all incidence of reported congenital malformations in upstate New York was 10.6 per 1,000 live births. Some differences between the two sets of data occurred: the upstate New York series had a higher incidence of spina bifida, hydrocephalus, congenital heart disease, evisceration of abdominal contents, tongue tie, torticollis, tumors, and "other" deformities of legs, arms, hands and feet; the New York City series had a higher incidence of "other" malformations of the central nervous system, "other" malformations of the genitourinary system, and the various kinds of dactylism. To what these differences are related is not known.

Of the 1,501 children reported in New York City to have a congenital malformation, 1,027 (68%) were children delivered by a private physician in a hospital, and 453

(30%) were delivered on a ward service in a hospital. The remaining 2% were delivered at home by private physicians, ambulance physicians and midwives. Thus, a community handicapped children's program in New York City which provides payment for the care of children with congenital malformations might reasonably be expected to cover all the 30% delivered on ward service of a hospital, most of the 2% delivered at home, and an unknown number of the 68% of the cases delivered on the private service of hospitals.

The incidence of reported congenital malformations in babies delivered of the private and ward service mothers is approximately the same—9.5 per 1,000 live births in the

TABLE 2

CONGENITAL MALFORMATIONS, MORE FREQUENT TYPES OF DEFORMITY, INCIDENCE AND NEONATAL MORTALITY, NEW YORK CITY—1951

Type	No. Reported	Incidence/1,000 Live Births	Neonatal Deaths	Neonatal Mortality Per Cent
Club foot	351	2.16	18	5.1
Adactylism, polydactylism or syndactylism	205	1.26	10	4.9
Cleft palate and/or cleft lip	128	0.79	15	11.7
Cleft lip, alone	53	0.32		
Cleft palate, alone	34	0.21		
Cleft palate and cleft lip, alone	27	0.17		
Cleft palate with other anomalies*	14	0.09		
Hypospadias	100	0.61	4	4.0
Spina bifida	73	0.45	16	21.9
Mongolism	46	0.28	9	19.6
Hydrocephalus	36	0.22	12	33.3
Anencephaly	34	0.21	34	100.0
Congenital heart disease	32	0.20	13	40.6
Erythroblastosis	30	0.18	11	36.7
Meningocele and encephalocele	29	0.18	10	34.5
Hemangioma and nevus	30	0.18	2	6.7
Imperforate anus	16	0.10	11	68.8

* Includes absence of extremities, evisceration, polydactylism, club foot, absent eye and ear, hydrocephalus, mongolism, hypospadias, adactylism.

private group and 8.6 in the ward service group. The numbers in the home delivered group are too small to draw conclusions, although the incidence is approximately the same (table 3). Maternal nutrition is generally thought to be less adequate in the ward service group, particularly in patients attending municipal hospitals in the City. If this opinion is correct, one can ask if maternal nutrition plays a significant role in the etiology of congenital malformations; no information is available on the reporting of congenital malformations in the ward service and private patient groups.

There were 128 infants reported with cleft palate and/or harelip, the over-all incidence being 0.79 per 1,000 live births (table 1). The incidence of cleft palate with or without harelip was 0.47 per 1,000 live births (table 2). The incidence of reported cleft palate and/or harelip of infants delivered in hospitals by private physicians was 0.92 per 1,000 live births, as compared with an incidence of 0.54 in the general service hospital group.

TABLE 3

INCIDENCE OF CONGENITAL MALFORMATIONS AND BIRTH INJURIES BY PLACE AND TYPE OF SERVICE AT BIRTH, NEW YORK CITY—1951

Place and Type of Service	Live Births			Congenital Malformations						Birth Injuries					
				No.			Incidence/1,000 Live Births			No.			Incidence/1,000 Live Births		
Hospital Deliveries	160,397			1,480			9.2			370			2.3		
A. Private patients		107,903			1,027			9.5			244			2.3	
Voluntary			72,389			648			9.0			137			1.9
Proprietary			35,514			379			10.7			107			3.0
B. General service patients		52,494			453			8.6			126			2.4	
Voluntary			24,172			242			10.10			54			2.2
Municipal			25,863			200			7.7			69			2.7
Federal			2,444			11			4.5			3			1.2
State			15			—			—			—			—
Nonhospital Deliveries	2,358			21			8.5			7			3.0		
Private Patients		548			6			10.9			2			3.6	
Ambulance Service		1,531			11			7.2			5			3.3	
Midwives		21			4			190.5			—			—	
Other		258			—			—			—			—	
Totals	162,755			1,501			9.2			377			2.3		

TABLE 4

CONGENITAL MALFORMATIONS AND BIRTH INJURIES, INCIDENCE AND NEONATAL MORTALITY, BY BIRTH WEIGHT
NEW YORK CITY—1951

Birth Weight (gm.)	Live Births		Congenital Malformations				Birth Injuries			
			No. Children with Reported Cong. Malformations		Incidence/1,000 Live Births	No. Neonatal Deaths	Neonatal Mortality Per Cent	No. Children with Birth Injury	Incidence/1,000 Live Births	No. Neonatal Deaths	Neonatal Mortality Per Cent
1,000 or less	842		11		13.1	10	90.9	—	—		
1,001–1,500	954	14,197	27	258	28.3 18.2	16	59.3	4	4.2		
1,501–2,000	2,418		54		22.3	30	55.6	5 32	2.1 2.3		
2,001–2,500	9,983		166		16.6	40	24.1	23	2.3	5	21.7
2,501–3,000	37,084		359		9.7	54	15.0	49	1.3	6	12.2
3,001–3,500	65,441		524		8.0	39	7.4	132	2.0	10	7.8
3,501–4,000	36,034	147,689	252	1,229	7.0 8.3	9	3.6	102 337	2.8 2.3	3	2.9
4,001–4,500	7,815		74		9.5	7	9.5	42	5.4		
4,501–5,000	1,214		10		9.2	3	30.0	7	5.8		
over 5,000	101		10		99.0	0	0	5	49.5	1	20.0
Unknown	869		14		25.3	10	71.4	8	9.2	1	12.5
Totals	162,755		1,501		9.2	218	14.5	377	2.3	26	6.9

Ninety-nine babies (77.4%) were delivered on hospital private services, 28 (21.9%) on hospital general services, and one infant was delivered at home.

Table 4 shows the birth weight distribution of the babies reported to have been born with congenital malformations, and the incidence of reported malformations in the conventional birth weight groups. As would be expected, the incidence in the prematurely born group (18.2 per 1,000 live births) is twice that in the nonpremature group (8.3), a difference which is statistically significant. In the three highest weight groups of premature infants, the incidence of reported malformations decreases as the weight of the infant increases. The lowest weight group has the lowest reported incidence; this may correctly reflect the incidence or may be due to the fact that in these smallest infants emphasis is placed on emergency care of the baby and not on a complete physical examination immediately after birth.

The incidence of reported congenital malformations in the white group (9.2 per 1,000 live births) is approximately the same as that of the nonwhite group (9.5). The reported incidences of cleft palate in the white and nonwhite groups statistically do not differ—0.82 and 0.59 per 1,000 live births, respectively. Certain conditions seem to be higher in the white—e.g., club foot and hypospadias. For example, the reported incidence of club foot is 2.30 per 1,000 live births in the white group (320 cases) and 1.30 in the nonwhite (31 cases). For hypospadias, the reported incidence in the white group is 0.69 per 1,000 live births (96 cases) and 0.17 in the nonwhite (4 cases). No valid conclusion can be drawn as to whether this is a chance occurrence or whether there is a color differential. On the other hand, polydactylism does show a statistically significant color difference; in the white group the reported incidence is 0.58 for 1,000 live births (80 cases) as compared with the reported incidence of 4.00 in the nonwhite (95 cases). This color difference is not found in adactylism or syndactylism, or in the other frequent types of congenital malformations listed in table 2.

Birth Injuries

In 1951, a total of 377 children was reported to have a birth injury, a reported incidence of 2.3 per 1,000 live births. Of this number, 189 children (50.1%) were reported with severe injury—fractures, paralysis and intracranial injury or hemorrhage. The incidence of children with reported severe birth injury for 1951 was 1.16 per 1,000 live births—similar to that reported in the City in 1948 and 1949.[3] In the paralysis group, the common types, as would be expected, were facial, brachial and Erb's paralysis. In the fracture group the commoner bones involved were clavicle and humerus (table 5).

A comparison of these 1951 New York City data with the upstate New York data of 1940-42 reveals considerable differences between the two sets of data. The over-all incidence of reported birth injury in upstate New York was 7.5 per 1,000 live births, more than three times the incidence in New York City. The incidence of every individual type of birth injury in the upstate group was higher than in the New York City series. A possible explanation for this difference may be the improvement in obstetric practice in this 11 year period, or a difference in obstetric practice between upstate New York and New York City, or a difference in reporting.

Of the 377 children reported in New York City to have a birth injury, 244 (64.7%) were children delivered by a private physician in a hospital, and 126 (33.4%) were delivered on a ward service in a hospital. The remaining 1.9% were delivered at home by a private physician or ambulance physician. Thus, a community handicapped children's

TABLE 5

BIRTH INJURIES BY TYPE AND SITE, INCIDENCE AND NEONATAL MORTALITY
NEW YORK CITY—1951

Type	No. Reported	Incidence/1,000 Live Births	Neonatal Deaths	Neonatal Mortality Per Cent
Paralysis	104	0.64	8	7.7
Facial	74			
Erb's	16			
Brachial	9			
Miscellaneous	5			
Fractures	61	0.37	1	1.6
Clavicle	31			
Lower extremity	14			
Humerus	12			
Upper extremity	4			
Intracranial injury or hemorrhage	24	0.15	10	41.7
Miscellaneous*	188	1.15	7	3.7
Totals	377	2.31	26	6.9

* Composed of contusions, abrasions, forceps marks, hematoma, lacerations (158 infants) and a heterogeneous group (30 infants).

program in New York City, which provides payment for the care of children with birth injury, might reasonably be expected to cover all of the 33% delivered on ward service of a hospital, most of the 2% delivered at home, and an unknown amount of the 65% delivered on the private service of hospitals.

The incidence of reported birth injury in babies delivered of private and ward service mothers is approximately the same—2.3 per 1,000 live births in the private group and 2.4 in the ward service group (table 3).

Data on an analysis of possible preventable factors in severe birth injuries reported in New York City in 1948 have already been published.[3]

In contrast to the situation in congenital malformations, the incidence of reported birth injuries in the prematurely born group is the same as that in the nonpremature group (table 4). The incidence of reported birth injuries in the white group is approximately the same as that of the nonwhite group, as it was in the group with congenital malformations.

NEONATAL DEATHS AND MORTALITY RATES

In New York City, physicians attribute the cause of neonatal deaths to birth injuries in 15% of the deaths and to congenital malformations in 15%, according to data on the cause of death submitted on death certificates filed with the Department of Health. Approximately 40% of the babies who die during the neonatal period are autopsied. Furthermore, there has been no decline in the neonatal deaths attributed to these two causes in New York City within recent years.[4]

Congenital Malformations

The neonatal mortality rate in the group with reported congenital malformations is 145 per 1,000 live births, or eight times the city-wide neonatal mortality rate for all live births. The neonatal mortality rate in the prematurely born group with reported congenital malformations is 372 per 1,000 live births or three times that of all prematurely live born infants in the city. The neonatal mortality rate in the full-term group with reported congenital malformations is 92 per 1,000 live births or 13 times that of all full-term live born infants in the City. The neonatal mortality rate in the prematurely born group with reported congenital malformations is four times that of the full-term group (table 1).

The neonatal mortality of the white group is 15.3% while that of the nonwhite group is 10.2%. This is of borderline significance. Further study of several years' experience is necessary.

Tables 1 and 2 present the neonatal mortality percents in the broad groups and more frequent types of reported congenital malformations. From a preventable point of view, these are certain items of interest. The question might be raised if some of the 69% of the imperforate anus cases, the 37% of the erythroblastosis cases, and the 12% of the cleft palate or harelip cases which terminated fatally might not have survived under more appropriate circumstances. There were 34 neonatal deaths in the babies reported with club foot, dactylism, hypospadias and "hemangioma and nevus." This number is three times the expected number of deaths and may indicate that there may have been more serious associated malformations not reported at birth.

Birth Injuries

The neonatal mortality rate in the group with reported birth injury is 69 per 1,000 live births or almost four times the City-wide neonatal mortality rate for all live births. The neonatal mortality rate in the prematurely born group with reported birth injury is 156 per 1,000 live births, which is only slightly higher than that of all prematurely live born infants in the City. The neonatal mortality rate in the full-term group with reported birth injury is 59 per 1,000 live births or almost eight times that of all full-term liveborn infants in the City. The neonatal mortality rate in the prematurely born group with reported birth injury is almost three times that of the full-term group (table 5).

The neonatal mortality of the white group is similar to that of the nonwhite group.

Table 5 shows the neonatal mortality percent in the broad groups. As would be expected, almost half the babies reported with intracranial injury or hemorrhage died within the first month of life. There were 16 neonatal deaths in the babies with reported fractures, paralysis and miscellaneous injuries. This number is twice the expected number of deaths and may indicate that there may have been more serious associated injuries not reported at birth.

Discussion

The data presented are helpful in planning services for children reported to have birth injuries and congenital malformations, since the reported incidence of broad categories and individual conditions is now known for the entire community. Guides have now been obtained for certain specific services.

Previously, the program of the New York City Department of Health which pays for

hospital, convalescent and rehabilitation care of certain kinds of children with handicaps —orthopedic, congenital cardiac, orthodontia and plastic surgical—did not include children with other types of congenital malformations, although the upstate New York program has included such children for a number of years. In the fall of 1952, the New York City program was expanded to include children with other types of congenital malformations which are amenable to surgical correction.

For example, because it is now known that there are at least approximately 130 babies born alive each year with cleft palate or harelip in New York City, a basis now exists for the planning of centers in hospitals for the complete rehabilitation of these children, of which in any one year there would be a total of approximately 2,700 under 21 years of age. One such center now exists, and plans are under way for a few additional centers which will provide surgical repair, pediatric evaluation and supervision, orthodontia, prosthodontia, dental care, speech therapy, psychologic and psychiatric assistance, audiometric testing and otologic service, and social service.

Previously, the New York City Department of Health provided one other direct service to these babies—namely, a visit by a public health nurse to the home to certain of the babies with congenital malformations. Babies with birth injuries were not included. Four categories of babies delivered on ward service were selected for such visiting—spina bifida, cleft palate, club foot and congenital dislocation of the hip. This group consisted of approximately 150 babies, or 10% of all the babies reported after birth to have congenital malformations in New York City. This plan is now being extended to include all newborn infants reported to have birth injuries or congenital malformations in New York City. In planning the extension of this service, a method is being simultaneously developed to analyze the value and effectiveness of the service. Essentially the analysis will attempt to answer three basic questions: (1) Did these babies have the condition they were reported to have on their birth certificates? (2) Were these babies already under good medical and/or hospital care? (3) If the babies were not under such care, what results were accomplished by having a public health nurse visit the home? To the authors' knowledge, no such evaluation of this kind of home visiting has been done.

The fact that there was no difference in the reported incidence of congenital malformations in babies born on the ward and private services of hospitals is an interesting finding. Certainly it is contrary to the general findings of the classical studies on maternal nutrition conducted by various investigators (Burke, Beal, Kirkwood and Stuart,[5] Ebbs et al.[6]). This finding in New York City should be followed by a study of maternal nutrition of private and ward service patients in New York City before any conclusions can be drawn.

Summary

1. In 1951, a total of 1,501 children was reported to have been born alive with one or more congenital malformations, an over-all reported incidence of 9.2 per 1,000 live births.

a. Two-thirds of the babies were delivered by a private physician in a hospital, and one-third on a ward service in a hospital. The incidence in the two groups and in white and nonwhite babies was approximately the same. However, the incidence in babies weighing less than 2,500 gm. was twice that in those babies weighing more.

b. Club foot, dactylism, cleft palate and/or harelip, and hypospadias were the most frequent types of congenital malformations reported, accounting for 78% of the total.

c. There were 128 babies reported with cleft palate and/or harelip, an over-all incidence of 0.79 per 1,000 live births.

d. The effect on neonatal mortality is presented.

2. In 1951 a total of 377 children was reported to have been born alive with one or more birth injuries, an over-all reported incidence of 2.3 per 1,000 live births. One half were reported with severe birth injury. The reported incidence was the same regardless of type of patient (private or ward service), color, or birth weight.

3. The 1951 data for New York City are compared with similar data for upstate New York for 1940-1942. The over-all incidence in reported congenital malformations in the two groups is similar, although some differences occurred in the frequency of individual malformations. The over-all incidence of reported birth injury in upstate New York was more than three times that in New York City; the incidence of each type of birth injury was higher in the upstate group.

4. The use of such data in planning services for these children in a community is discussed.

References

1. De Porte, J. V., and Parkhurst, E., Congenital malformations and birth injuries among children born in New York State, outside of New York City, in 1940-1942, New York State J. Med. **45**:1097, 1945.
2. Lilienfeld, A. M., Parkhurst, E., Patton, R., and Schlesinger, E. R., Accuracy of supplemental medical information on birth certificates, Pub. Health Rep. **66**:191, 1951.
3. Gold, E. M., Clyman, M., Wallace, Helen M., and Rich, H., Study of some obstetric factors in birth injuries and of value of birth certificate reporting of birth injuries in New York City, Obst. & Gynec. **1**:431, 1953.
4. Wallace, Helen M., and others, Recent trends in maternal and perinatal mortality in New York City, to be published.
5. Burke, B. S., Beal, V. A., Kirkwood, S. B., and Stuart, H. C., Nutrition studies during pregnancy, Am. J. Obst. & Gynec. **46**:38, 1943.
6. Ebbs, J. H., and others, Influence of improved prenatal nutrition upon infant, Canad. M. J. **46**:6, 1942.

Spanish Abstract

Malformaciones Congénitas y Lesiones al Nacimiento en la Ciudad de Nueva York

Desde 1948 se introdujo en la ciudad de Nueva York la ley de que en las actas de nacimiento se anotaran tanto las lesiones por traumatismo del parto como las malformaciones congénitas. El valor de estos datos es lo que se trata de analizar en el presente estudio, considerando dos los fines principales de los informes oficiales:

1. Ayudar a conocer la magnitud de un problema particular de salud pública para proveer a la comunidad con las atenciones adecuadas, y

2. Servir como medio de localizar al paciente individual que padece tal problema de salud y por lo tanto poder dar los pasos necesarios para su cuidado especializado.

Previamente el Departamento de Salud de la Ciudad de Nueva York ayudaba en los problemas de hospitalización, convalescencia y rehabilitación de algunos problemas de la infancia (ortopédicos, cardiacos congénitos, ortodóncicos y quirúrgico-plásticos), olvidándose de otras malformaciones congénitas. A fines de 1952 el programa de la ciudad se extendió tanto a otros tipos de malformaciones susceptibles de corrección quirúrgica, como a lesiones por traumatismo al nacer. Al mismo tiempo que se extendía este programa, se vino desarrollando un método de trabajo que analizara el valor y efectividad de tal servicio, basándose en las tres preguntas básicas siguientes:

1. Los niños considerados con estas malformaciones lo tienen señalado en su certificado de nacimiento?

2. Estaban estos niños ya bajo un cuidado médico y/o de hospital considerado bueno?

3. Si no lo estaban, qué resultados se obtuvieron con la visita a domicilio de la enfermera sanitaria?

En 1951 se reportaron 1501 niños con una o más malformaciones congénitas, dando una incidencia de 9.2 por mil nacimientos vivos; la incidencia fue semejante en los niños blancos y de color, en los niños atendidos en hospitales privados o en hospitales generales, pero dos veces mayor en los prematuros. Las malformaciones más frecuentemente vistas y que dieron el 78% del total, fueron los pie bott, dactilismo, paladar hendido con y sin labio leporino, e hipospadias. 128 niños presentaron paladar hendido con o sin labio leporino, dando una incidencia de 0.79 por mil nacimientos vivos. Los médicos de Nueva York creen que las lesiones obstétricas contribuyeron en un 15% y las malformaciones congénitas en otro 15% a las muertes del recién nacido.

En 1951 se reportaron 377 niños nacidos vivos con una o más lesiones al nacer, dando una incidencia de 2.3 por mil nacidos vivos; de éstos, la mitad presentaron lesión severa; la incidencia fue la misma para los servicios privados y generales, la raza y el peso de nacimiento.

La incidencia total de malformaciones congénitas para la ciudad de Nueva York en 1951 y la del Estado de Nueva York de 1940 a 1942 (excluyendo la ciudad) es la misma, aun cuando se observan diferencias en la frecuencia de malformaciones específicas individuales. En cambio la correspondiente a las lesiones al nacer es más de tres veces mayor en el estado que en la ciudad de Nueva York, siendo además la incidencia de cada tipo individual de lesión, mayor en el grupo del estado.

125 Worth Street

PSEUDOCHOLEDOCHAL CYST

By ARTHUR G. SMITH, *Captain,* USAF (MC), AND SAM F. SEELEY,
Brig. General, USAF (MC)
Washington, D.C.

CHOLEDOCHAL cyst, or idiopathic cystic dilatation of the common bile duct, has been long recognized and reported by a number of authors.[1-8] The term pseudocholedochal cyst is being applied to a fibrous-walled, bile-containing cyst within the peritoneal cavity resulting from injury to the common duct and presenting many of the clinical features of a choledochal cyst. Since an exhaustive search of the literature has failed to disclose such a condition, the following case report seems justified.

CASE REPORT

A 14 wk. old white boy was admitted with transfer diagnosis of cirrhosis of the liver and ascites. The birth history was normal in all respects. Birth weight was 3.6 kg. The infant seemed to be in good health until 3 wk. of age at which time he gradually developed postprandial vomiting, diminished frequency of stools, and weight loss. Four days after the onset of symptoms, a diagnosis of congenital hypertrophic pyloric stenosis was made and he was admitted to a hospital where a pyloromyotomy was performed. No complications were reported and the pyloric musculature was described as being moderately hypertrophied. Postoperatively, the patient did well until the tenth day when vomiting, diarrhea, anorexia, lethargy and a low-grade fever occurred. Thirty-six hours later, jaundice, clay-colored stools and dark urine were first noticed and became more marked during

FIG. 1. Patient before removal of pseudocholedochal cyst. Note distention of abdomen, prominence of abdominal veins, and emaciation of extremities.

the next several days. About 3 wk. after the onset of these signs and symptoms, generalized abdominal swelling was noticed. The swelling progressed and was associated with dyspnea until a paracentesis was performed 6 wk. after the pyloromyotomy. The paracentesis yielded 1000 cc. "amber-colored" fluid with a specific gravity of 1.009. Culture of this fluid was negative. Following this procedure his dyspnea lessened until the abdomen rapidly became swollen again. Repeat paracenteses 4 and 5 wk. later yielded 1300 cc. and 600 cc., respectively of "amber-colored" fluid.

From the Pediatric Section, Medical Service, Walter Reed Army Hospital, Washington, D.C.
(Received for publication May 1, 1953.)

Cirrhosis of the liver with ascites was suspected and the patient was transferred here for further studies and treatment.

Physical examination at the time of admission revealed a pale, emaciated infant with a symmetrically distended abdomen (Fig. 1). His temperature was 37.2°C., his weight, 3.7 kg. Chest circumference was 36 cm. and abdominal circumference, 49 cm. An abdominal examination revealed dilated veins and the entire abdomen was flat to percussion, with no shifting dullness or evidence of a fluid wave. Liver was not felt, but the spleen was palpable. Skin was pale and loose with no evidence of icterus. The remainder of the physical examination was essentially normal.

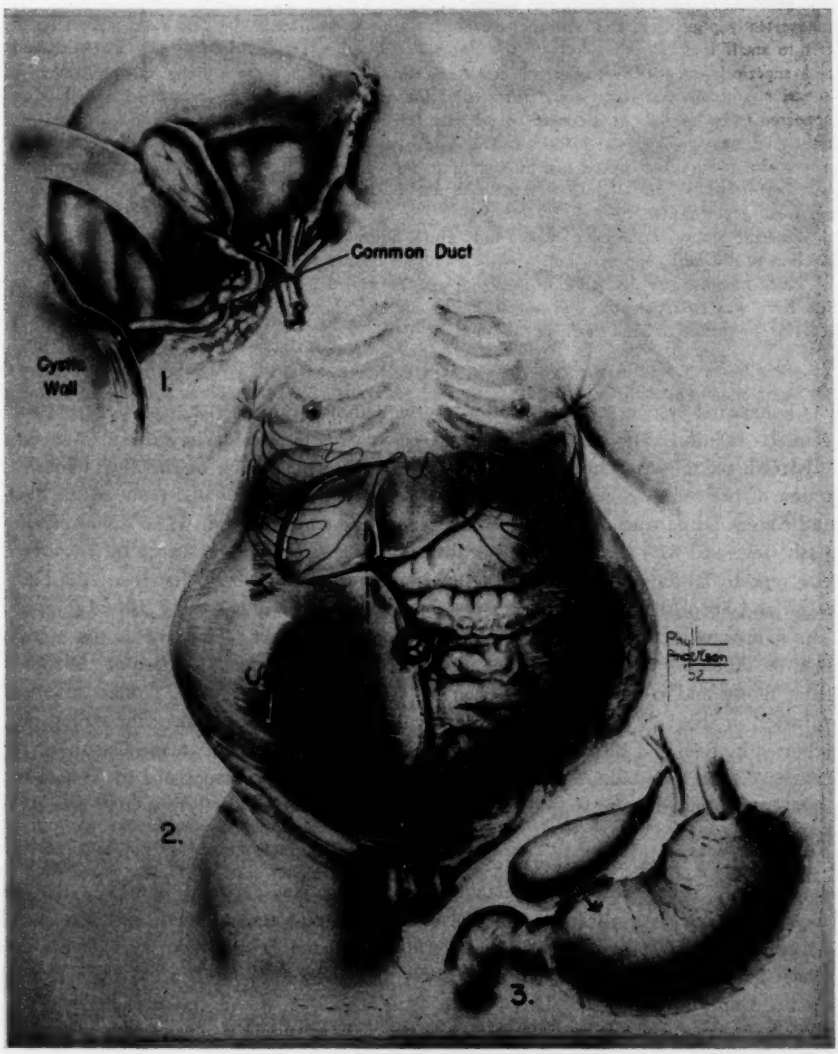


FIG. 2. Panel 1 illustrates transected end of common bile duct at lateral border of liver. Panel 2 illustrates extent of intact cyst, extending over superior surface of liver. Panel 3 illustrates side-to-side cholecystogastrostomy which was performed after removal of cyst.

Chest roentgenogram was normal and the abdominal RGs showed a large soft tissue density measuring 20 by 9 cm. which occupied most of the right side of the abdomen, and displaced the small intestines to the left of the midline.

There was increasing respiratory distress and a paracentesis yielded 1000 cc. dark green fluid that foamed readily when shaken. The specific gravity of this fluid was 1.009 and the bilirubin content was 4.4 mg. direct, 2.0 mg. indirect. Smear and culture of this fluid were negative. The following day a repeat paracentesis was performed, with 250 cc. similar dark green fluid being obtained. The specific gravity was 1.009. One week after admission an exploratory abdominal operation was performed. The peritoneum was opened revealing a friable and ill-defined cyst wall which was inadvertently punctured, and 550 cc. dark green fluid was aspirated. The cyst was adherent on the left to small intestines, inferiorly to the sigmoid and cecum, on the right to parietal peritoneum, and superiorly to the liver. Careful dissection showed that the cyst actually extended over the superior, anterior, and right lateral surfaces of the liver. The gallbladder was filled with bile and appeared to be normal. At the right lateral edge of the liver, the end of the proximal segment of a transected common duct was identified. The distal segment of the common duct could not be found. The common duct was ligated just proximally to the site of transection and a cholecystogastrostomy was performed. Figure 2 illustrates the cyst, the position of the common duct, and the type of anastomosis performed.

A needle biopsy of the liver showed mild portal fibrosis with moderate bile duct proliferation. At the time of discharge, approximately 5 wk. after admission, his weight was 4.7 kg.

Three months after discharge, at 8 mo. of age, he weighed 7.7 kg. and, with the exception that the liver was still palpable one fingerbreadth, and the spleen 2 fingerbreadths below the costal margins, he seemed to be in excellent condition.

Discussion

Choledochal cyst, or cystic dilatation of the common bile duct, is regarded as a congenital condition. The exact pathogenesis is not certain, but favored theories include valviform reduplication of the duct wall with consequent closure of the duct, abnormal course of the common duct through the duodenal wall, weak muscular tissue of the duct, and congenital narrowing of the duct as it enters the duodenum.[1] In 1932 Zinninger and Cash[2] reviewed 82 cases and in 1943 Shallow[3] reviewed 175 cases. Since then scattered case reports have appeared, so that the total number is still probably less than 200. Dickinson and Spencer[4] in 1952 added a case report and reviewed the usual clinical findings. The symptoms usually appear in the first few years of life but seldom within the first six months. About 75% of the cases have been reported in females. The triad of abdominal pain, tumor and jaundice have all been emphasized in the literature. A mass has been palpated in about 70% of the cases. The cysts vary a great deal in size; the largest one, reported by Reel and Burrell,[5] contained 8 l. of bile. No cases of spontaneous cure of the cyst have been reported. According to Gross,[6] side-to-side anastomosis of the cyst to the duodenum is usually the simplest technical operation and has the lowest operative mortality.

A search of the medical literature has failed to reveal a single case of "pseudocholedochal cyst." The preoperative diagnosis on the patient reported here was that of choledochal cyst. Not until the proximal end of the transected common duct was found adjacent to the liver border was it realized that the cyst had formed to wall off the bile which had emptied into the peritoneal cavity. Microscopic examination of the cyst wall disclosed only fibrous tissue. This finding alone, however, would not rule against a true choledochal cyst, since in many case reports the walls of the choledochal cysts were comprised of fibrous tissue and were devoid of endothelium.

The manner in which this patient's common duct was injured never could be ascertained

and still remains a matter of speculation. The distal segment of the severed duct could not be located because of the large amount of dense fibrous tissue surrounding the duodenum. Also because of this, it seemed more efficacious to do a cholecystogastrostomy rather than to try to mobilize the duodenum for a cholecystoduodenostomy.

Summary

A case of a fibrous-walled, bile-containing cyst in an infant, secondary to injury to the common duct, is presented. Since this is believed to be the first such case to appear in the medical literature, the term pseudocholedochal cyst is suggested. A brief review of the clinical picture of choledochal cyst is given, since the findings in this case, and in the reported cases of true choledochal cysts, are similar.

References

1. Gilliland, M. B., Holloway, C. E., and Lange, J. H., Congenital choledochus cyst, review of literature and case report with one-year postoperative follow-up, J. Pediat. **37**:387, 1950.
2. Zinninger, M. M., and Cash, J. R., Congenital cystic dilatation of common bile duct, Arch. Surg. **24**:77, 1932.
3. Shallow, T. A., Eger, S., and Wagner, F., Jr., Congenital cystic dilatation of common bile duct, Ann. Surg. **117**:355, 1943.
4. Dickinson, E. H., and Spencer, F. C., Choledochal cyst, report of case with unusual features, J. Pediat. **41**:462, 1952.
5. Reel, P. J., and Burrell, N. E., Cystic dilatation of common bile duct, Ann Surg. **75**:191, 1922.
6. Ladd, W. E., and Gross, R. E., Abdominal Surgery of Infancy and Childhood, Philadelphia & London, W. B. Saunders Company, 1941, p. 278.
7. Gross, R. E., Idiopathic dilatation of common bile duct in children, J. Pediat. **3**:730, 1933.
8. Hutchins, E. H., and Mansdorfer, G. B., Congenital cystic dilatation of common bile duct with sequelae, J.A.M.A. **125**:202, 1944.

Spanish Abstract

Quiste Pseudo-Colédoco

El quiste colédoco o dilatación quística idiopática del colédoco ha sido descrito en muchas ocasiones, siendo aceptado como una entidad nosológica definida; en este informe los autores utilizan el término de quiste pseudo-colédoco para designar un quiste fibroso con contenido biliar que encontraron en la cavidad peritoneal de un lactante, probablemente formado por alguna lesión al conducto colédoco. Las manifestaciones clínicas del presente caso son semejantes a las señaladas para los quistes colédocos verdaderos. Los autores lo consideran el primero que se presenta en la literatura médica, al no hallarlo descrito en la revisión bibliográfica que hicieron.

Se trata de un niño blanco de 14 semanas de edad que llegó a sus manos con el diagnóstico de cirrosis del hígado y ascitis. A las 4 semanas de edad se había practicado en el paciente pilorotomía, en virtud de presentar desde los 20 días de edad, vómitos, tendencia a la constipación y pérdida de peso; el píloro fué considerado como moderadamente hipertrófico. Diez días más tarde se presentaron nuevamente los vómitos, acompañados de diarrea, anorexia, febrícula, ictericia y evacuaciones de color mastique, seguidas a las tres semanas por distensión abdominal y acumulación de ascitis en grandes cantidades, que obligaron a paracentesis repetidas sin ninguna mejoría; se le diagnóstico cirrosis del hígado y ascitis y se le envió al Hospital del Ejército "Walter Reed."

Aquí se repitieron las paracentesis en varias ocasiones, obteniéndose siempre un líquido verde obscuro; al practicarse laparotomía exploradora en virtud de la formación sostenida del líquido intraabdominal, se localizó un quiste que contenía 550 c.c. de líquido también verde obscuro. El quiste se adhería a los intestinos, al peritoneo y al hígado; se disecó y aisló del conducto colédoco, que se ligó; se practicó entonces una colecistogastrostomía. Un mes después la prueba de la bromosulftaleína fue normal; la biopsia del hígado mostró ligera fibrosis portal con proliferación

moderada del cístico. Tres meses más tarde, el niño se encontró en buenas condiciones excepto en el sentido de que el hígado rebasada uno y el bazo dos traveses de dedo, el borde costal correspondiente.

Los autores insisten que la triada dolor abdominal, tumoración e ictericia en los primeros años de la vida pero excepcionalmente antes de los primeros 6 meses de edad, hablan a favor de quiste colédoco, del que se han reportado hasta la fecha alrededor de 200 casos. Al presente lo denominan quiste pseudo-colédoco, a pesar del cuadro clínico que obligó al diagnóstico preoperatorio de quiste colédoco, en vista de que su situación y constitución anatómica diferían del quiste verdadero.

Walter Reed Army Hospital

HORMONE PATTERNS IN PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA

By VINCENT C. KELLEY, M.D., PH.D., ROBERT S. ELY, M.D., AND RICHARD B. RAILE, M.D.*
Salt Lake City

RECENT demonstration of the efficacy of cortisone in the therapy of congenital adrenal hyperplasia[1-3] has focused attention anew on the peculiar endocrine abnormalities presented by patients with this syndrome. This approach to therapy was based on the postulation that administration of cortisone would suppress pituitary release of adrenocorticotrophin (ACTH) thereby diminishing the production of adrenal androgens. Inferential evidence of the validity of this hypothesis is furnished by the well substantiated fact that urinary 17-ketosteroid excretion although uniformly elevated in untreated patients with congenital adrenal hyperplasia,[1,4-6] is diminished by cortisone therapy.[1-3,7-9] The belief that steroids, including those normally inhibiting the production of ACTH, are deficient in patients with congenital adrenal hyperplasia has been substantiated by the demonstration[9] that these children have exceptionally low circulating levels of 17-hydroxycorticosteroids and, compared to normal children, an inability to respond to ACTH administration by an elevation of these 17-hydroxycorticosteroid levels.[10]

Direct confirmation of the existence of increased concentrations of ACTH in the blood of untreated patients with congenital adrenal hyperplasia and suppression of these levels during cortisone therapy has until recently been unattainable since no satisfactory technic was available for the determination of endogenous ACTH in the blood of human subjects. This deficiency in methodology has been overcome by Sydnor and Sayers'[11] modification of the adrenal ascorbic acid depletion method[12] by a preliminary concentration of the blood ACTH, employing the principle of the oxycellulose technic of Astwood et al.[13] for the isolation of ACTH. With this technic it has been demonstrated that children with congenital adrenal hyperplasia have elevated circulating levels of endogenous ACTH and that these levels become undetectable during cortisone therapy.[14]

In the present study urinary excretion of 17-ketosteroids and circulating concentrations of 17-hydroxycorticosteroids have been determined in patients with congenital adrenal hyperplasia before and during cortisone therapy† and after its temporary discontinuation. These data are compared with results previously reported[14] concerning blood ACTH titers in the same patients.

MATERIALS AND METHODS

Of the 8 children with congenital adrenal hyperplasia employed in this study, there were 7 with female pseudohermaphrodism and one with macrogenitosomia praecox. One additional child with

From the Lockhart Memorial Laboratory, Department of Pediatrics, University of Utah College of Medicine, Salt Lake City.

(Received for publication April 15, 1953.)

* Present address: Department of Pediatrics, University of Minnesota Hospitals, Minneapolis.

† Cortisone used in this study was supplied through the courtesy of Merck & Company, Inc., Rahway, N.J.; ACTH (Acthar®), through the courtesy of the Armour Laboratories, Chicago.

male pseudohermaphrodism was included for comparison. The patients with congenital adrenal hyperplasia received cortisone, intramuscularly or orally, in doses varying from 12.5 to 50 mg./day during therapy periods. However, cortisone was withheld for at least 24 hr. before each study performed during these periods.

The 24 hr. urinary 17-ketosteroid excretions were measured by the method of Callow, Callow and Emmens[15] and by a modification of the method of Cahen and Salter.[16] The circulating levels of 17-hydroxycorticosteroids were determined by the method of Nelson and Samuels.[17] The dose of ACTH used (given intramuscularly) for the 17-hydroxycorticosteroid response tests was 25 I.U. in most instances, and 100 I.U. in a few. Blood samples were obtained immediately before and 2 hr. after the injection of ACTH for determination of 17-hydroxycorticosteroid concentrations. Plasma 17-hydroxycorticosteroid concentrations were determined before and at 2, 8 and 24 hr. after the administration of the first dose of cortisone in 5 patients with congenital adrenal hyperplasia (3 children given cortisone 50 mg. intramuscularly and 2 given 100 mg. orally).

Observations

Table 1 compares the effects of cortisone therapy on circulating concentrations of 17-hydroxycorticosteroids and endogenous ACTH, and on urinary excretion of 17-ketosteroids in patients with congenital adrenal hyperplasia. During the pretherapy period the endogenous ACTH levels and 17-ketosteroid excretion values are elevated, while the circulating concentrations of 17-hydroxycorticosteroids are exceptionally low. During the period of cortisone therapy the ACTH levels are no longer detectable and the 17-ketosteroid excretion approaches normal. In patients given intramuscular cortisone the 17-hydroxycorticosteroid concentrations increase to approximately average normal values. This increase reflects measurement of the administered cortisone.[9] However, patients receiving oral cortisone therapy have low levels of 17-hydrocorticosteroids on test days during the therapy period. This is not an unexpected finding, since, as mentioned above, cortisone was withheld for at least 24 hours before each test was performed. The demon-

TABLE 1

Effects of Cortisone Therapy in Congenital Adrenal Hyperplasia on Circulating 17-Hydroxycorticosteroids and Endogenous ACTH and on Urinary 17-Ketosteroids

Therapy Status	Blood ACTH*			Urinary 17-ketosteroids mg./day			Plasma 17-Hydroxycorticosteroids μg./100 cc.		
	No. Pts.	No. Assays	Mean† ±S.E.M.	No. Pts.	No. Samples	Mean ±S.E.M.	No. Pts.	No. Samples	Mean ±S.E.M.
Before cortisone therapy	5	5	54.0 ±8.30	7	28	23.3 ±7.12	6	26	3.1 ±0.66
During cortisone therapy	5	7	−6.0 ±5.16	7	92	3.0 ±1.15	4‡	23	8.7 ±1.16

* Data previously published.[14]

† Expressed as adrenal ascorbic acid depletion in mg. ascorbic acid/100 gm. (Concentration of ascorbic acid in left adrenal removed prior to injection of blood eluates minus the concentration in the right adrenal removed 1 hr. later.) For doses of blood eluates used and responses to standard doses of ACTH on corresponding days see reference 14.

‡ Following the intramuscular administration of cortisone. (In 8 determinations on 2 patients on oral cortisone, which was discontinued 24 hr. prior to blood sampling, the average 17-hydroxycorticosteroid concentration was 1.6±0.87 μg./100 cc.)

TABLE 2

RESPONSE OF PLASMA 17-HYDROXYCORTICOSTEROIDS (μg./100 cc.) TO SINGLE DOSE OF CORTISONE IN UNTREATED PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA

Oral (100 mg.)					Intramuscular (50 mg.)				
Patient	Time				Patient	Time			
	0 hr.	2 hr.	8 hr.	24 hr.		0 hr.	2 hr.	8 hr.	24 hr.
F.P.	5.5	70	4.9	0	R.Wi.	4.7	24.1	—	21.1
J.C.	2.2	103	9.7	0	E.Wi.	1.6	21.1	—	15.8
					W.C.	2.0	7.5	3.9	4.3
Mean	3.9	87	7.3	0	Mean	2.8	17.6	—	13.7

stration has been made previously[18] in normal individuals given cortisone orally that the elevated 17-hydroxycorticosteroid concentrations which result disappear within several hours. The data in table 2 indicate that patients with congenital adrenal hyperplasia behave similarly in this regard. In this table are shown the 17-hydroxycorticosteroid plasma concentrations before and at 2, 8 and 24 hours after the administration of a test dose of cortisone in each of five untreated patients with congenital adrenal hyperplasia. In two patients given cortisone 100 mg. orally high plasma concentrations of 17-hydroxycorticosteroids were observed at two hours after the administration of the test dose. By eight hours these concentrations had returned nearly to the base-line value and at 24 hours had become zero in both patients. In 2 of 3 patients given cortisone 50 mg. intramuscularly moderate elevations of the plasma 17-hydroxycorticosteroid concentrations were observed two hours after administration of the test dose and these concentrations still were elevated moderately 24 hours after administration of the cortisone. In the third patient (W. C.), a considerably larger child, only a slight elevation of the 17-hydroxycorticosteroid concentration occurred at two hours after administration of the test dose and by eight hours the concentration of these steroids in the plasma had returned nearly to the initial value.

The effects of cortisone therapy in an illustrative patient, E. W., are shown in chart 1. The excretion of 17-ketosteroids was high prior to therapy, decreased to normal for her age during therapy, increased when therapy was discontinued, and decreased again when therapy was re-instituted. No ACTH assay was performed prior to therapy. However, after three months of therapy, assay revealed an undetectable concentration of ACTH. Two assays performed at 4 and 8 weeks after discontinuation of therapy showed elevated levels of ACTH. Again, 4 weeks after re-institution of therapy there was no detectable level of ACTH. The 17-hydroxycorticosteroid concentrations were exceptionally low prior to therapy, increased during therapy, decreased during the period of temporary discontinuation of therapy, and increased again after therapy was re-instituted.

The data of table 3 illustrate the adrenal cortical unresponsiveness to the injection of ACTH (Acthar®) in children with congenital adrenal hyperplasia as compared to normal children. Neither prior to nor during cortisone therapy is there any increase in 17-hydroxycorticosteroid levels in this group of patients in response to the injection of

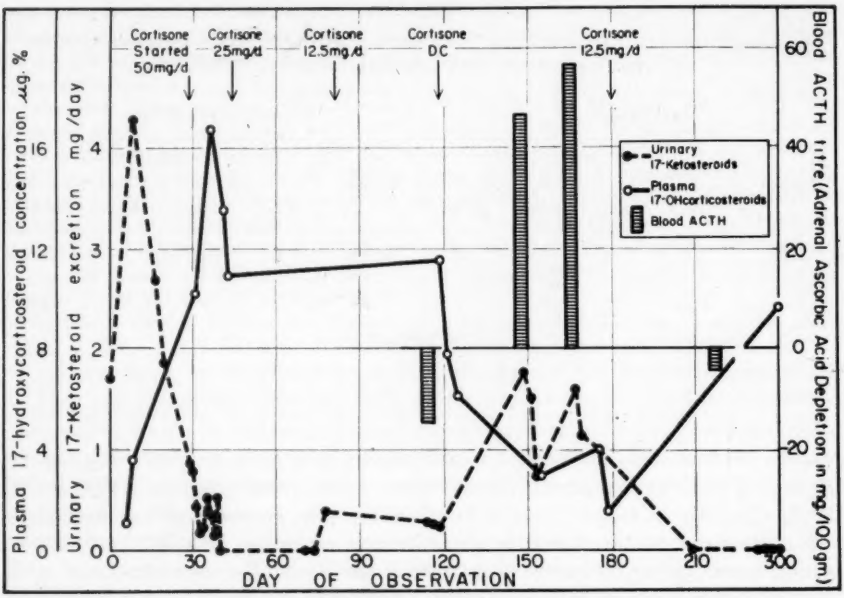


CHART 1. Effects of cortisone therapy in patient with congenital adrenal hyperplasia.

ACTH whether a test dose of 25 I.U. or of 100 I.U. ACTH is given. This is in contrast to the response observed in a control group of children who show a mean elevation in these levels of 23.5 ± 3.65 µg./100 cc. Thus, the decreased adrenal responsiveness of patients with congenital adrenal hyperplasia is apparent even when a stimulating dose of ACTH is employed which is four times the dose that consistently evokes significant 17-hydroxycorticosteroid response in a control group of children.

TABLE 3

ACTH-17-HYDROXYCORTICOSTEROID RESPONSE IN PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA

Therapy Status	Test Dose ACTH (I.U.)	No. Patients	No. Responses	17-Hydroxycorticosteroids (µg./100 cc.)		
				0 hr. (Mean)	2 hr. (Mean)	Change (Mean ± S.E.M.)
Controls*	25	19	30	13.0	36.5	23.5±3.64
Before cortisone therapy	25	4	5	3.1	2.5	−0.6±1.53
	100	5	6	2.2	2.6	0.4±0.05
	25 or 100	6	11	2.6	2.6	0 ±0.68
During cortisone therapy	25	5	13	5.6	4.1	−1.5±1.27
	100	3	6	5.9	4.2	−1.7±1.65
	25 or 100	5	19	5.7	4.2	−1.5±0.99

* See reference 10.

TABLE 4

ACTH-17-HYROXYCORTICOSTEROID RESPONSE IN PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA RECEIVING CORTISONE THERAPY
(Influence of Route of Cortisone Administration)

Type cortisone therapy	No. Patients	No. Responses*	17-Hydroxycorticosteroids (μg./100 cc.)		
			0 Hr. (Mean)	2 Hr. (Mean)	Change (Mean ± S.E.M.)
I.M.	4	14	7.0	5.3	−1.7±1.30
Oral	2	5	2.2	0.9	−1.3±1.12

* Responses both to 25 I.U. and to 100 I.U. ACTH are included.

In table 4 data are presented which indicate that the route of administration of cortisone therapy does not influence significantly the 17-hydroxycorticosteroid response to ACTH. Despite the difference in control levels, neither the patients receiving oral nor those receiving intramuscular cortisone therapy exhibit an increase in the plasma levels of these steroids in response to the injection of either 25 or 100 I.U. ACTH.

In contrast to the adrenal unresponsiveness of patients with female pseudohermaphrodism, one patient recently observed with male pseudohermaphrodism (diagnosis established by laparotomy and biopsy) exhibited normal adrenal responsiveness. This patient's plasma 17-hydroxycorticosteroid concentration increased from a control level of 20.7 μg./100 cc. to a two hour value of 45.5 μ.g./100 cc. in response to a test dose of 25 I.U. ACTH. Thus, not only was the response to ACTH adequate but the control level was high normal in contrast to the low values observed in patients with female pseudohermaphrodism. In addition, two determinations of 24 hour 17-ketosteroid excretion in this patient yielded values of 0 and 0.2 mg./day in contrast to the increased excretion of these steroids observed in patients with female pseudohermaphrodism. Clinically this six year old child showed no evidence of sexual hair, voice changes, or increased skeletal or somatic growth.

DISCUSSION

The hormone pattern of decreased 17-hydroxycorticosteroid and increased endogenous ACTH plasma concentrations and increased urinary 17-ketosteroid excretion observed in children with congenital adrenal hyperplasia before treatment is in agreement with the hypothesis of Wilkins[1] and of Bartter.[7] This postulation considers the excessive production of androgen precursor to occur as a result of excessive pituitary secretion of ACTH. This excess in ACTH secretion occurs because the concentration of those corticosteroids normally inhibiting the pituitary release of ACTH is not increased sufficiently by ACTH stimulation to function effectively as a control over further ACTH release. The rationale of cortisone therapy is dependent upon the ability of cortisone to inhibit the release of ACTH and through this mechanism to depress the exaggerated production of androgen precursors. This rationale is supported by the ACTH assay data obtained on the blood eluates of patients receiving cortisone therapy, showing elevated concentrations of ACTH in the precortisone therapy period and contrastingly low concentrations during the period of therapy.

It appears conclusive that certain steroids are being produced in insufficient amounts by the adrenal cortex in response to the high levels of circulating ACTH. The concentrations of circulating 17-hydroxycorticosteroids in these patients are uniformly low except when supplemented by exogenous cortisone. Moreover, the failure of these 17-hydroxycorticosteroid levels to become elevated in response to the injection of ACTH, whether before or during the period of cortisone therapy, reveals an adrenal unresponsiveness with respect to these steroids.

The pattern of abnormal endocrine function of such patients would appear to be as follows: The adrenal cortex responds to circulating ACTH stimulation by producing primarily androgen precursors. Only small quantities of 17-hydroxycorticosteroids are produced. Since these steroids are the normal inhibitors of ACTH secretion the latter is now released in excessive amounts. This causes greater stimulation of the adrenal cortex and, in turn, excessive production of androgen precursors without a corresponding increase in 17-hydroxycorticosteroid production. The resultant endocrine pattern shows elevated concentrations of endogenous circulating ACTH, elevated urinary excretion values of 17-ketosteroids and low concentrations of circulating 17-hydroxycorticosteroids. Inasmuch as the adrenal cortex of a child with congenital adrenal hyperplasia, in contrast to that of a normal child, cannot respond to the injection of exogenous ACTH by an elevation of the 17-hydroxycorticosteroid level the presumption is that the primary abnormality resides in the adrenal cortex.

The ACTH-17-hydroxycorticosteroid response test provides a chemical technic in addition to that of the 17-ketosteroid excretion for differentiating female pseudohermaphrodism from male pseudohermaphrodism. In the latter condition there is no adrenal dysfunction and both normal 17-ketosteroid excretion and normal 17-hydroxycorticosteroid response to ACTH occur. As the plasma 17-hydroxycorticosteroid response test is applicable in early infancy it enables such differentiation to be made at a time when 17-ketosteroid excretion may not have become abnormal as yet.

Summary

Measurements of plasma 17-hydroxycorticosteroid concentration and urinary 17-ketosteroid excretion were made in children with congenital adrenal hyperplasia. These results have been compared with blood ACTH titers in the same children. Prior to cortisone therapy endogenous ACTH concentrations and 17-ketosteroid excretion were abnormally high whereas circulating 17-hydroxycorticosteroid concentrations were exceptionally low. During the period of cortisone therapy these values approached normal. Adrenal unresponsiveness to ACTH was evidenced in patients with congenital adrenal hyperplasia by their failure to produce elevations of circulating 17-hydroxycorticosteroid concentrations in response to ACTH injection.

Acknowledgment

The authors gratefully acknowledge the technical assistance of Mary C. O'Brien, Doris F. Tippit, Margaret G. Anderson and H. Beth Dowding.

References

1. Wilkins, L., and others, Treatment of congenital adrenal hyperplasia with cortisone, J. Clin. Endocrinol. 11:1, 1951.
2. Wilkins, L., Lewis, R. A., Klein, R., and Rosemberg, E., Suppression of androgen secretion by cortisone in case of congenital adrenal hyperplasia, Bull. Johns Hopkins Hosp. 86:249, 1950.

3. Wilkins, L., Lewis, R. A., Klein, R., and Rosemberg, E., Die Wirkung von Cortisone auf die Ausscheidung der 17-Ketosteroids und anderer Steroide bei Patienten mit Kongenitaler Niebennierenhyperplasie, Helvet. paediat. acta **5**:418, 1950.
4. Wilkins, L., Hyperadrenocorticism, PEDIATRICS **3**:533, 1949.
5. Kepler, E. J., and Locke, W., in Williams, R. H., Textbook of Endocrinology, Philadelphia, W. B. Saunders Company, 1950, pp. 180-248.
6. Wilkins, L., Klein, R., and Lewis, R. A., Response to ACTH in various types of adrenal hyperplasia, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote. Philadelphia, The Blakiston Company, 1950, p. 184.
7. Bartter, F. C., and others, Effects of adrenocorticotropic hormone and cortisone in adrenogenital syndrome associated with congenital adrenal hyperplasia: Attempt to explain and correct its disordered hormonal pattern, J. Clin. Investigation **30**:237, 1951.
8. Shephard, T. H., II, and Clausen, S. W., Case of adrenogenital syndrome with hypertension treated with cortisone, PEDIATRICS **8**:805, 1951.
9. Kelley, V. C., Ely, R. S., and Raile, R. B., Metabolic studies in patients with congenital adrenal hyperplasia: Effects of cortisone therapy, J. Clin. Endocrinol. & Metab. **12**:1140, 1952.
10. Kelley, V. C., Ely, R. S., Raile, R. B., and Bray, P. F., Comparison of eosinophil and circulating 17-hydroxycorticosteroid response to epinephrine and ACTH, Proc. Soc. Exper. Biol. & Med. **81**:611, 1952.
11. Sydnor, K. L., and Sayers, G., Technic for determination of adrenocorticotrophin in blood, Proc. Soc. Exper. Biol. & Med. **79**:432, 1952.
12. Sayers, M. A., Sayers, G., and Woodbury, L. A., Assay of adrenocorticotrophic hormone by adrenal ascorbic acid-depletion method, Endocrinology **42**:379, 1948.
13. Astwood, E. B., Raben, M. S., Payne, R. W., and Grady, A. B., Purification of corticotropin with oxycellulose, J. Am. Chem. Soc. **73**:2969, 1951.
14. Sydnor, K. L., and others, Blood adrenocorticotrophin in children with congenital adrenal hyperplasia, Proc. Soc. Exper. Biol. & Med. **82**:695, 1953.
15. Callow, N. H., Callow, R. K., and Emmens, C. W., Colorimetric determination of substances containing grouping—CH_2CO—in urine extracts as indication of androgen content, Biochem. J. **32**:1312, 1938.
16. Cahen, R. L., and Salter, W. T., Urinary 17-ketosteroids in metabolism. I. Standardized chemical estimation, J. Biol. Chem. **152**:489, 1944.
17. Nelson, D. H., and Samuels, L. T., Method for determination of 17-hydroxycorticosteroids in blood: 17-hydroxycorticosterone in peripheral circulation, J. Clin. Endocrinol. & Metab. **12**: 519, 1952.
18. Raile, R. B., Ely, R. S., and Kelley, V. C., Studies of 17-hydroxycorticosteroids in children. II. Response of blood levels to injection of certain hormones, J. Pediat. **42**:46, 1953.

SPANISH ABSTRACT

Patrones Hormonales en Pacientes con Hiperplasia Suprarrenal Congénita

El empleo de la cortisona en la terapéutica de la hiperplasia suprarrenal congénita ha causado nuevo interés en el estudio de las anormalidades endócrinas peculiares a los pacientes con este síndrome; tal empleo se basa en la idea de que la cortisona suprimiría la producción de adrenocorticotrofina (HACT) por la hipófisis y por lo tanto se abatiría la producción de andrógenos suprarrenales. En efecto, la excreción de los 17-ketoesteroides urinarios, elevada en pacientes no tratados, disminuye con la administración de cortisona. Asímismo se han visto niveles plasmáticos bajos de 17-hidroxicorticosteroides en niños con hiperplasia suprarrenal congénita y falta de respuesta con elevación de sus niveles al emplearse en ellos HACT, lo que demostraría que hay deficiencia de esteroides en tales pacientes.

En este estudio se han determinado en pacientes con hiperplasia congénita suprarrenal la excreción urinaria de 17-ketoesteroides y las concentraciones circulantes de 17-hidroxicorticosteroides, antes y durante el tratamiento con cortisona y después de suspenderlo. De los 8 niños estudiados 7 presentaban pseudo hermafroditismo femenino y uno macrogenitosoma precoz; se incluye para comparación, otro caso de pseudo hermafroditismo masculino. Se les administró cortisona por vía intramuscular u

oral a dosis variables de 12.5 y 50 miligramos por día, durante los períodos de tratamiento, que se suspendió por lo menos 24 horas antes de cada determinación. Se empleó HACT por vía intramuscular u oral a dosis de 25 U.I. en la mayor parte de los casos y 100 U.I. para unos cuantos, a fin de investigar la respuestas de los 17-hidroxicorticosteroides.

Las determinaciones de la concentración plasmática de los 17-hidroxicorticosteroides y la excreción urinaria de los 17-ketoesteroides mostraron los siguientes datos: antes del tratamiento con cortisona, las concentraciones de HACT endógeno y la excreción de los 17-ketoesteroides eran anormalmente elevados mientras que los 17-hidroxicorticosteroides circulaban a niveles sumamente bajos; durante el tratamiento con cortisona estas cifras se normalizaban; no se observó respuesta suprarrenal al HACT, según lo demostró la incapacidad de los pacientes para producir elevación en las concentraciones de los 17-hidroxicorticosteroides circulantes después de la inyección del HACT.

En pacientes con hiperplasia congénita suprarrenal, la disfunción endócrina presentaría las siguientes características: la corteza suprarrenal responde a la estimulación por el HACT circulante produciendo fundamentalmente precursores de andrógenos, y los 17-hidroxicorticosteroides sólo en pequeñas cantidades; puesto que estos esteroides son los inhibidores normales de la secreción de HACT, ésta circula en cantidades excesivas, lo que a su vez causa mayor excitación de la corteza suprarrenal y por lo tanto se producen mayor cantidad de precursores andrógenos sin el aumento correspondiente de la producción de 17-hidroxicorticosteroides. El patrón endócrino resultante muestra concentraciones elevadas del HACT endógeno circulante, excreción urinaria elevada de 17-ketoesteroides y baja concentración de los 17-hidroxicorticosteroides circulantes. Como la corteza suprarrenal del niño con hiperplasia congénita suprarrenal, contrastando con la de un niño normal, no responde a la inyección de HACT exógeno con el aumento del nivel de los 17-hidroxicorticosteroides, se supone que la anormalidad fundamental radica en la corteza suprarrenal.

La prueba HACT-17-hidroxicorticosteroides nos da una técnica química para diferenciar el pseudo hermafroditismo femenino del masculino; en éste no hay disfunción suprarrenal y presenta tanto la excreción normal del 17-ketoesteroides como respuesta normal al HACT de los 17-hidroxicorticosteroides; como esta última prueba se puede realizar tempranamente, la diferencia entre los dos tipos de pseudo hermafroditismo puede también efectuarse en una época en que aún no se tiene una excreción anormal de los 17-ketoesteroides.

1940 South Second East

ABNORMAL ELECTROLYTE COMPOSITION OF SWEAT IN CYSTIC FIBROSIS OF THE PANCREAS

Clinical Significance and Relationship to the Disease

By PAUL A. DI SANT'AGNESE, M.D., ROBERT C. DARLING, M.D., GEORGE A. PERERA, M.D., AND ETHEL SHEA, B.A.
New York City

KESSLER and Andersen[1] in 1952 reported that 5 of 10 children admitted to Babies Hospital as a result of a severe hot spell in August 1948 were children with cystic fibrosis of the pancreas. All the patients reported had severe dehydration and vasomotor collapse. Only one fatal case had hyperpyrexia, two were recorded as having perspired freely before admission and the skin was clammy on admission in at least one other. Laboratory data were few but two serum chlorides determinations disclosed abnormally low values. It was pointed out by Kessler and Andersen that patients with fibrocystic disease of the pancreas tend to respond adversely to heat during periods of high atmospheric temperature, although the mechanism responsible for this unusual susceptibility was not clear.

Since there was already some evidence that in fibrocystic disease of the pancreas there may be a disturbance of multiple glandular structures and since the sweat glands enter into the physiologic picture in a major way only during hot weather, the plan of the present study was as follows: (a) measure the amount and electrolyte composition of sweat in patients with this condition; (b) attempt to relate the findings to the clinical heat casualties and to the pathologic physiology of the disease. Some of the results discussed in this paper have been reported elsewhere in preliminary form.[2]

METHODS AND SELECTION OF CASES

Two groups of cases were studied. Forty-three patients with cystic fibrosis of the pancreas, ranging in age from 2 to 16 yr., were compared to 50 controls. The latter included 40 children, 1½ to 16 yr. old, and 10 adults from 35 to 62 yr. of age.

Of the first group, 38 presented the classical clinical and laboratory features of cystic fibrosis of the pancreas. In all of these children one or more duodenal assays had shown an absence of pancreatic enzymes. Five have died subsequent to these studies. Autopsy was performed in 4 and all showed the changes typical of the disease. In the remaining 5 of the 43 patients some pancreatic activity either was present at the time of study or had been present in earlier years and then disappeared. The diagnosis, however, was strongly suspected on the basis of the family history, the chronic pulmonary involvement, and in 4 out of 5 the abnormal character of the stools, as well as steatorrhea and azotorrhea on chemical examination of the feces.

The second (control) group included a variety of types of cases on the wards of Babies and

---

From the Departments of Pediatrics, Physical Medicine and Rehabilitation, and Medicine of the College of Physicians and Surgeons, Columbia University, and the Babies Hospital and Presbyterian Hospital, New York City.

Supported in part by a grant from the Baruch Committee for Physical Medicine and in part by a gift for Celiac Research from the United Fruit Company and in part by the Robert Bacon Whitney fund for cystic fibrosis of the pancreas.

Presented at the May 1953 meeting of the American Pediatric Society, Atlantic City, N.J.

(Received for publication May 13, 1953.)

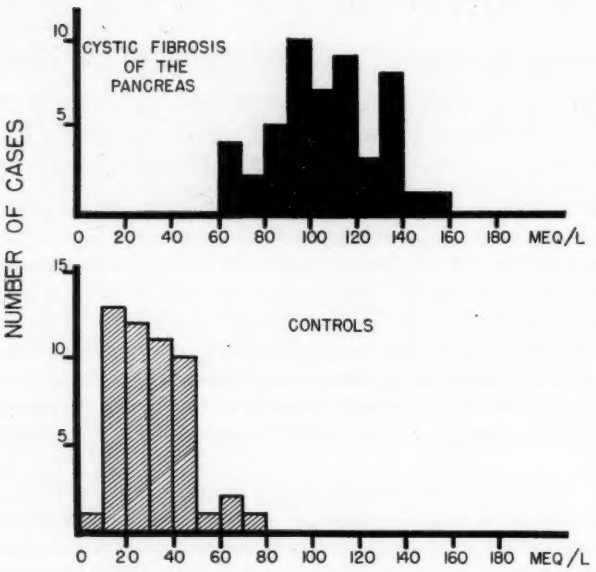


CHART 1. Abdominal sweat chloride in 43 patients with cystic fibrosis of pancreas (50 determinations) and 50 controls.

Presbyterian Hospitals with the following specifically excluded: patients with known adrenal insufficiency or kidney disease and members of the families of known patients with cystic fibrosis of the pancreas.

No patient in either group had been receiving ACTH or cortisone or salicylates for the few weeks prior to the "sweat test," and none had fever at the time.

Each patient was subjected to a standard thermal stress lying quietly in a room maintained at 32.2°C. and about 50% humidity, for a period of 1 to 2 hr. Each of the subjects was covered similarly with a sheet and blanket. Sweat was collected by a method previously described by one of the authors.[3] It consisted of the application of a dry gauze square patch of 12 sq. cm. in area, covered with impermeable plastic and sealed at the edges by waterproof adhesive tape. At the end of the collection period the patch was lifted, all visible moisture removed by the gauze square, which was then immediately placed in a stoppered flask previously weighed with the dry sponge. The flask with the sweat-soaked gauze was then re-weighed. To the flask was added a measured volume of $LiSO_4$ solution and, after leaching, aliquots were analyzed for chloride by the method of Keys[4] and for sodium and potassium with the flame photometer.

Sweat was obtained in all cases from the midabdomen as it was shown in preliminary experiments that this area tends to give more constant results in a given individual and is technically more suitable in young children. The choice of the abdominal skin area was justified also *a priori* by the fact that the skin temperature of the trunk is much more constant than that of the extremities. The skin temperature is one of the important variables apparently controlling the electrolyte composition of sweat.[5] It is worth while to recognize that the methods of sweat collection in this study were unavoidably arbitrary in part. It was technically impossible under the conditions of this study to collect a representative sample of total thermal sweat. Sweat from the abdominal wall represented the 50 to 60% of thermal sweat which is formed on the trunk,[6] was presumably free of the secretions of the

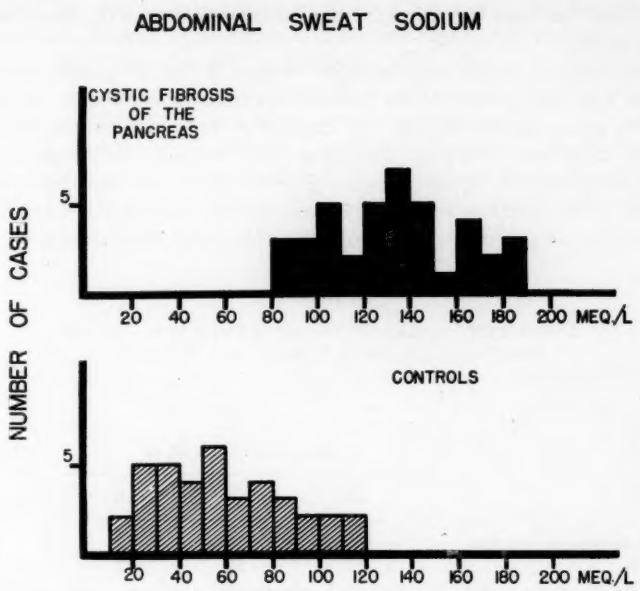

ABDOMINAL SWEAT SODIUM
CYSTIC FIBROSIS OF THE PANCREAS
NUMBER OF CASES
5
20 40 60 80 100 120 140 160 180 200 MEQ./L
CONTROLS
5
20 40 60 80 100 120 140 160 180 200 MEQ./L

CHART 2. Abdominal sweat sodium in 35 patients with cystic fibrosis of pancreas (40 determinations) and 38 controls.

apocrine glands (chiefly axillary and groin) which are not concerned primarily in thermal control,[7] and therefore this site seemed to be the best practical compromise for testing. For the sake of accuracy in all instances, 2 separate patches were applied, one on either side of the abdomen, and the collected sweat analyzed separately. The sweating rates are reported per unit of body surface (12 sq. cm.) which is the customary physiologic type of unit.

The thermal stimulus was not only constant for all patients, but very mild. In fact it has been shown repeatedly that if a severe enough thermal stimulus is given the electrolyte content of sweat can be increased in normal individuals and that its sodium concentration rises directly with the rate of excretion as well as with an elevation of skin or rectal temperature.[5, 8]

Finally, no reason was found to believe that age or color makes a difference in the volume of composition of sweat.

RESULTS

A. Abnormal Electrolyte Composition of Sweat: Charts 1 and 2 present the data obtained on determination of the sodium and chloride content of abdominal sweat in 43 patients with cystic fibrosis of the pancrease and 50 controls. The difference between the electrolyte concentration of the sweat in fibrocystic disease of the pancreas as compared with other subjects is highlighted by the markedly different distribution of values. The wide range of spread in values for both groups is likewise shown.

The range for the abdominal sweat chlorides of patients with cystic fibrosis of the pancreas was from 60 to 160 mEq./l. sweat with a mean of 106. For the controls the figures were from 4 to 80 mEq. with an average value of 32. There was almost no overlap, with no fibrocystics below 60 and the great majority above 80 and only 3 of the 50 controls above 60 mEq. Furthermore, one of these three controls possibly had fibrocystic disease of the pancreas but lacked some of the criteria required for a diagnosis of this disease, and another was recovering from tuberculous meningitis. Evidence of a salt-

losing syndrome has been found in the latter condition[9] although the sweat has not been specifically studied.

The sweat sodium content was also quite different in the two groups. The range for the patients with cystic fibrosis of the pancreas was from 80 to 190 mEq./1. with a mean of 133. The spread for the controls was from 10 to 120 mEq. with an average of 59. There were no patients with fibrocystic disease below 80 and only 9 controls above this value; an overlap of 23%. It should be mentioned in this respect that two of the patients in the latter group, controls with a high sweat sodium, possibly had fibrocystic disease of the pancreas and two others were recovering from tuberculous meningitis.

TABLE 1

ELECTROLYTE CONTENT AND VOLUME OF SWEAT IN 43 PATIENTS WITH CYSTIC FIBROSIS OF PANCREAS, AND 50 CONTROLS

	Sweat			
	Mean Values in mEq./l.			Mean Volume
	Cl	Na	K	(Gm./hr./12 cm.²)
Cystic Fibrosis of Pancreas	106	133	18	0.104
Controls	32	59	12	0.142
Difference (△.M.)	74	74	6	0.038
S.E.△.M.	4	6.4	1.08	0.020
$\frac{\triangle.M.}{S.E.\triangle.M.}$	18	11	5.5	1.9
Probability (P.)	$\ll.001$	$\ll.001$	$<.001$	—
No. of Observ. C.F. of P.	50*	40	40	49
No. of Observ. Controls	50	38	38	49

* Sweat was analyzed on 2 separate occasions in 7 patients with cystic fibrosis of the pancreas.

Table 1 presents a statistical analysis of the graphic material just shown. The mean values for electrolyte content and volume of abdominal sweat for both patients with cystic fibrosis of the pancreas and controls are listed along with differences of the means, their standard errors and the statistical significance in terms of probability.

The difference in the mean values for sodium and chloride content of sweat in patients with fibrocystic disease of the pancreas and controls is of great statistical significance. The difference of the mean values for potassium content of sweat in the two groups is less, but still of marked significance.

The mean volume of sweat in gm./hour/12 sq. cm. was not significantly different in the two groups. It was evident from a study of the figures that there was great variation among individuals and at different times in the same individual, both in patients with fibrocystic disease of the pancreas and among controls, which confirms the findings of previous investigators.[8] The standard deviations were ±0.082 gm. of sweat for fibrocystic disease of the pancreas and ±0.137 for the controls. The high volumes occasionally encountered among the controls were not found in patients with fibrocystic disease of the pancreas. Thus one girl of 13 years with bronchial asthma had a sweat volume of 1.0

gm./hour/12 sq. cm., 10 times the mean and accounting alone for one-eighth the total volume of sweat obtained in 50 controls. If the few instances of unusually high volumes are excluded, there was virtually no difference in the amount of sweating in the two groups. There was, therefore, no evidence of any reduction in sweating in patients with cystic fibrosis of the pancreas as compared with other individuals.

Lack of Effect of Pancreatic Deficiency or Chronic Respiratory Involvement Per Se or Drug Administration on Electrolyte Composition of Sweat: Several questions may be raised immediately. One of them is: What effect, if any, does pancreatic deficiency or chronic pulmonary disease have on the electrolyte composition of sweat?

TABLE 2

LACK OF EFFECT OF PANCREATIC AND RESPIRATORY INVOLVEMENT ON ELECTROLYTE COMPOSITION OF SWEAT

	Cystic Fibrosis of Pancreas (mean values)					Controls (mean values)				
	No. of Cases	Sweat (mEq./l.)			Pancr.* "Trypsin"		No. of Cases	Sweat (mEq./l.)		
		Cl	Na	K	(u./cc.)			Cl	Na	K
Group I	27	110	135	17	0					
" II	11	95	128	18	0	Group V	9	38	63	10
" III	3	100	119	25	263	" VI	11	28	61	15
" IV	2	118	132	18	216→31					
Mean of 43 cases		106	133	18	—	Mean of 50 cases		32	59	12

* Normal→100 u./cc.

To answer this question, patients with cystic fibrosis of the pancreas were divided into four groups and the mean values for abdominal sweat chlorides, sodium and potassium and for pancreatic "trypsin" as obtained by duodenal drainage are listed in table 2.

Group I, the largest with 27 cases, represents patients with complete pancreatic deficiency and moderate to severe respiratory involvement. None of these children was acutely ill at the time when their sweat was analyzed, and very few had CO_2 retention in the serum. None had uncompensated respiratory acidosis. In Group II are listed the values for 11 cases with complete pancreatic deficiency and little or no lung involvement. In Group III* are 3 children with partial or no pancreatic deficiency, but moderate to severe pulmonary disease and in Group IV* two patients in whom severe respiratory involvement preceded by months or years pancreatic insufficiency. Calculation showed no significant difference in sweat electrolyte values between any two of the four separate groups.

Two groups of controls are also listed in the same manner and in the same table 2.

* Although detailed descriptions of patients of these types are lacking in the literature, isolated examples have been recognized in several clinics. These 5 patients will be reported in a forthcoming publication. In 2 of these 5, recent autopsy data have confirmed the clinical diagnosis.

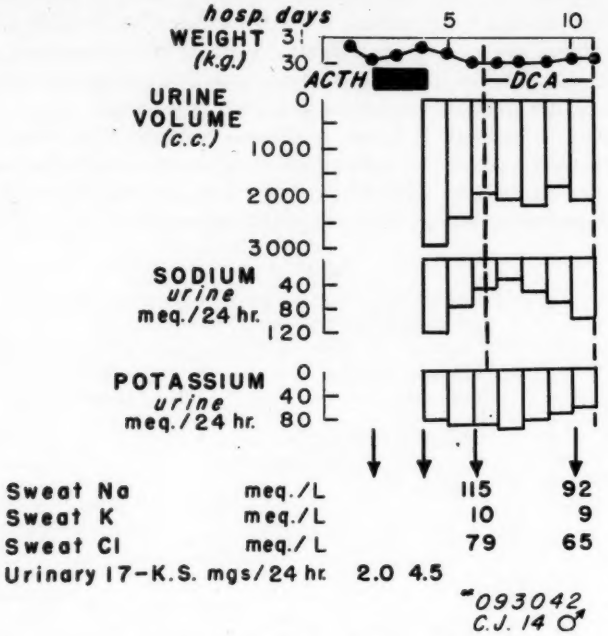


CHART 3. C. J., 14 yr. old male with cystic fibrosis of pancreas. Response of adrenals to administration of ACTH and of sweat electrolytes to administration of DCA.

In Group V are the mean values for sweat electrolytes of patients with various diseases of the pancreas. This includes four cases of total pancreatectomy, one of partial pancreatectomy with pancreatitis in the remainder of the pancreas, one of chronic pancreatitis with stone formation. All these patients had diabetes mellitus as well. Of the other three subjects two were children with diabetes mellitus and one a woman with an islet cell adenoma of the pancreas. Their average sweat electrolyte values were very close to the mean for the controls. In Group VI are given the mean values for sweat electrolytes for a group of 11 patients with chronic pulmonary diseases. This includes five patients with bronchial asthma and chronic bronchopneumonia. The other six had chronic lung disease of undetermined origin. Three of the latter patients had normal pancreatic enzymes by duodenal drainage, none had steatorrhea. The mean values for sweat chloride, sodium and potassium were close to the average figures for the controls.

As most of the patients with cystic fibrosis of the pancreas were getting pancreatic extracts (pancreatin) and many terramycin, it was felt necessary to prove that administration of these two drugs did not affect the electrolyte concentration of sweat. Accordingly, 10 such patients were taken off pancreatin for several days before a sweat test was done and the sweat was analyzed in seven fibrocystic patients who were not and had not been on terramycin or aureomycin for months or years. Sweat electrolytes in both groups were close to the mean for patients with the disease as a whole. It might be added that five control patients who had been on terramycin failed to show any elevation in sweat electrolytes.

B. Metabolic Studies of Adrenal and Kidney Function: It is an established fact that

adrenal insufficiency (Addison's disease) may lead to high chloride levels in the sweat.[10] It is also known that giving adequate amounts of desoxycorticosterone acetate (DCA) leads in these patients to a drop to normal or subnormal levels in sweat electrolytes and that in normal individuals either ACTH or DCA has a similar effect.

Accordingly, ACTH 25 mg. three times a day were administered intramuscularly for two days to a 14 year old prepubertal male with cystic fibrosis of the pancreas to determine whether his adrenals could respond (chart 3). The urinary 17-ketosteroids increased from 2 to 4.5 mg. per 24 hours. As a check ACTH was administered in the same manner and dosage to another 13 year old prepubertal male patient with fibrocystic disease of the pancreas (chart 5) and a similar increase in urinary 17-ketosteroids and a decrease in the total fasting eosinophile count from 75 to 31 were observed.

Five milligrams of DCA a day were then given subcutaneously for five days in the first metabolic study (chart 3). During this second period, sweat electrolytes responded by decreasing a little, but still remained in the high range.

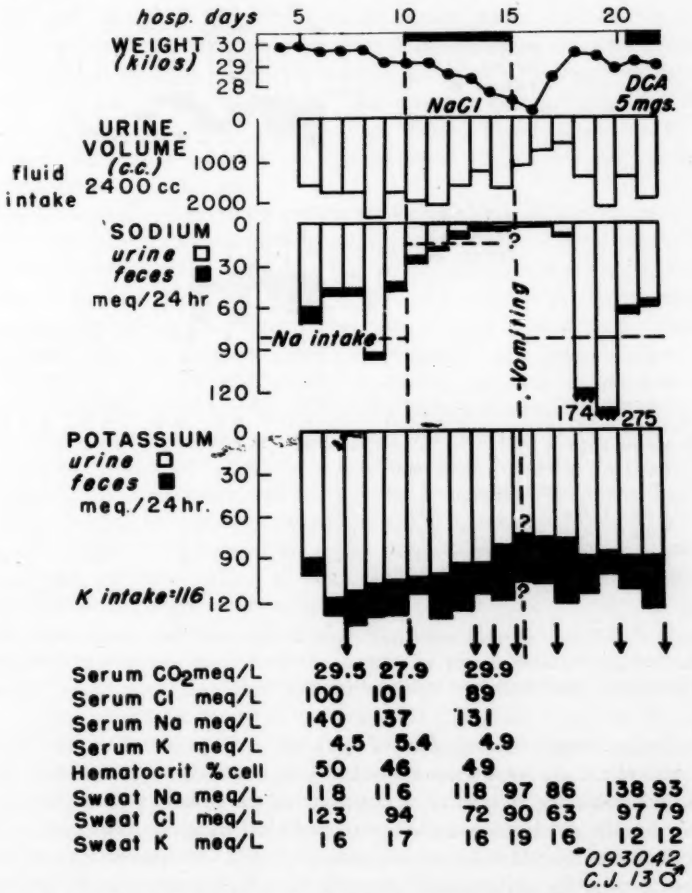

hosp. days 5 10 15 20
WEIGHT (kilos) 30 29 28
NaCl
DCA 5 mgs.
URINE VOLUME (c.c.) 0 1000 2000
fluid intake 2400 cc
SODIUM urine feces meq/24 hr 0 30 60 90 120
Na intake
Vom/ting
174
275
POTASSIUM urine feces meq./24 hr. 0 30 60 90 120
K intake 116
Serum CO2 meq/L 29.5 27.9 29.9
Serum Cl meq/L 100 101 89
Serum Na meq/L 140 137 131
Serum K meq/L 4.5 5.4 4.9
Hematocrit % cell 50 46 49
Sweat Na meq/L 118 116 118 97 86 138 93
Sweat Cl meq/L 123 94 72 90 63 97 79
Sweat K meq/L 16 17 16 19 16 12 12
093042
C.J. 13 ♂

CHART 4. C. J., 13½ yr. old male with cystic fibrosis of pancreas. Kidney, weight, serum and sweat electrolyte response to salt restriction (10th to 15th hospital day).

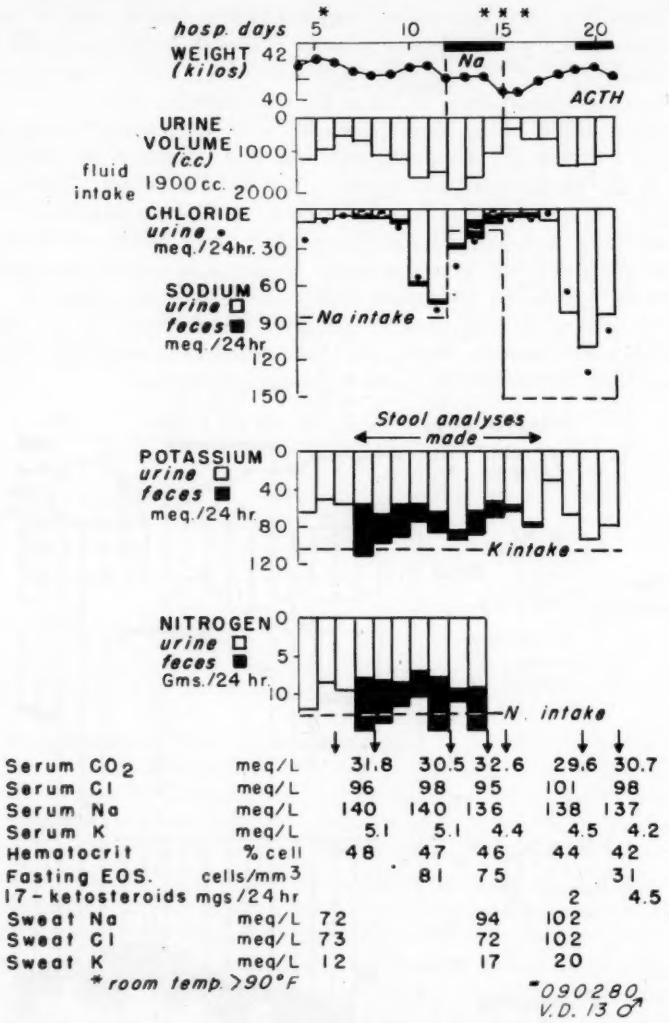


CHART 5. V. D., 13 yr. old male with cystic fibrosis of pancreas. Effect of hot weather and of salt restriction (12th to 15th hospital day) on excretion of sodium-chloride in urine, on body weight and on sweat electrolytes. Adrenal response to administration of ACTH.

In chart 4 are listed further studies for a 20 day metabolic period on the first patient. In order to indicate the total water and salt balance the following are shown: the body weight in kilograms, the 24 hour urine output in cc., the 24 hour sodium output in urine and stools in mEq./24 hours and the urinary and fecal potassium expressed in the same manner. The values for chlorides in both stools and urine were also determined and were quite close to those for sodium. For clarity they have been omitted. In the lower part of the same chart are listed the values for the serum and sweat electrolytes. The potassium

intake was 116 mEq./24 hours throughout. The basic sodium and chloride intake was 85 mEq./day (broken line), except for a "low salt" period from the 10th to the 15th hospital day when only 15 mEq. sodium-chloride were given/24 hours.

During the period of salt restriction the kidneys were able to reduce excretion of sodium and chloride amazingly well, so that by the third day the patient was excreting less salt in his stools and urine than he was taking by mouth. Despite this unusually good conservation of sodium chloride by the kidneys, the patient lost 2 kg. in weight, his serum chloride decreased from 100 to 89 by the fourth day and his serum sodium from 137 to 131 mEq./l. After five days he began to vomit and the experiment was discontinued. Such vomiting is quite characteristic of fibrocystic disease of the pancreas in acute salt loss during hot weather. The weather was warm (July 1952), although not unduly hot, and the salt was lost presumably through the sweat. Serial determinations of sweat electrolytes show that during salt restriction the patient was able to lower the salt concentration in sweat somewhat (e.g., sweat chloride from 94 to 72 mEq./l.), but not to normal levels.

Similar experiments during a 20 day metabolic period on V. D., another 13 year old male with cystic fibrosis of the pancreas, are recorded in chart 5. This chart is set up in a manner similar to the preceding one, but the values for urinary chlorides and the urine and fecal nitrogen are listed. A fecal fat balance indicating an average fecal fat content/24 hours of 12 gm. (56% of the intake absorbed) was also performed, but is not recorded. As in the previous experiment the basic sodium-chloride intake was 85 mEq. in the 24 hours and during the "low salt" period 15 mEq./day. However, salt restriction was carried out only for three days.

During the low-salt period (12th to 15th hospital day), the kidneys conserved sodium-chloride as efficiently as they did in the previous patient. Again, 1 kg. of weight (presumably extracellular fluid) was lost during this time and the serum electrolyte levels were beginning to decrease, although because of the short duration of the experiment they never reached the low levels of the previous case. A similar type of kidney response was observed during the first few days of the patient's hospital stay (without salt restriction) when the weather was hot (room temperature 32.2°C.) and salt was presumably lost in large amounts in the sweat. During this time the patient was receiving 85 mEq. sodium-chloride per day in his diet, but was putting out less than 10/24 hours in his urine and stools combined. This same fact should be kept in mind in evaluating the values for sweat electrolytes. Of the three determinations, only the last (on the 18th hospital day) can be said to have been performed when the patient was in approximately normal salt balance. Taking 102 mEq./l. as the baseline values for sweat sodium and chloride, it can then be seen that there was some decrease in sweat electrolytes during both periods of salt loss, but that these values still remained very high.

In the experiments recorded in charts 4 and 5, both patients, C. J. and V. D., failed to lose weight during the low salt periods for the first 24 and 48 hours, respectively. Although of doubtful significance, this is an unusual response as it has been previously shown[11] that an average of at least 0.8 kg. is lost by normal individuals during the first 24 hours of salt restriction. Following the end of the low salt diet and a period of salt retention by the kidneys for three days thereafter, there was a marked sodium and chloride diuresis. The diuresis assumed massive proportions in C. J. (chart 4), when 174 and 275 mEq. sodium were excreted on the 18th and 19th hospital day, respectively!

C. Electrolyte Abnormalities of the Serum: The effects of massive salt depletion of the body through the sweat in patients with fibrocystic disease of the pancreas can be detected in the serum electrolyte values under appropriate circumstances.

TABLE 3

SERUM ELECTROLYTES IN 47 PATIENTS WITH CYSTIC FIBROSIS OF PANCREAS

	Serum				
	pH	(mean values in mEq./l.)			
		CO_2	Cl	Na	K
I. Doing Well (31 cases)	7.38	24	100	138	4.4
II. Respiratory Acidosis (10 cases)	7.13 to 7.46	34	93	136	4.6
III. "Heat Casualties" (6 cases)	7.40	26	80	128	4.0

In table 3 are charted the mean values for serum pH and serum electrolytes for 47 patients with cystic fibrosis of the pancreas, subdivided as follows: 31 patients (43 determinations) in satisfactory clinical condition, 10 cases (26 determinations) in compensated or uncompensated respiratory acidosis and 6 so-called "heat casualties" (6 determinations).

Under normal circumstances the serum electrolytes in fibrocystic disease of the pancreas are within normal limits. In respiratory acidosis the compensatory mechanism for the accumulation of CO_2 in the serum is through excretion of chlorides by the kidney. Accordingly, the value for serum chlorides is low and that for CO_2 is high. The serum sodium is not affected, however, and its values are normal. The sum of the values for CO_2 and chlorides is about the same in Groups I and II, since the quantities of these two compounds in the serum are reciprocally affected.

In Group III the values for serum chloride and sodium are both greatly decreased, as might be expected in view of the abnormal composition of sweat. The values for CO_2 are normal. The sum of CO_2 and chloride in this third group is only 106 as compared with 128 and 127, respectively, for Groups I and II.

From the practical standpoint, a diagnosis of acute salt loss in a patient with CO_2 accumulation will necessitate the demonstration of a decreased serum sodium.

In table 4 are detailed the figures for serum electrolytes during the peak of acute salt loss in six patients with cystic fibrosis of the pancreas observed during the summer of 1952. Also tabulated are the values for sweat electrolytes after recovery in 5 of the 6 patients. On the left hand side of the same table are listed the seven steps leading from perspiration to death. High atmospheric temperature, especially sudden heat, causes profuse sweating, which in view of the abnormal sweat composition leads to acute salt loss. The dehydration which accompanies loss of sodium-chloride is made worse by vomiting, and if it reaches a sufficiently severe degree, hyperthermia and then coma and death follow in fairly rapid succession. None of the patients observed at Babies Hospital in the summer of 1952 died, although the first case was admitted in coma and moribund. This three year old child had perspired profusely for only one day and then began to vomit. A physician was called who withheld all fluids by mouth because of fear of intestinal obstruction. The patient deteriorated rapidly and was admitted in coma a few hours later. He responded well to massive intravenous fluid and electrolyte replacement, but his sensorium remained cloudy for several days and there was evidence of severe renal damage with the blood NPN rising

TABLE 4

"HEAT CASUALTIES" IN CYSTIC FIBROSIS OF PANCREAS

Name	Symptoms*	Electrolytes						
		Serum				Sweat†		
Age (yrs.)	1 2 3 4 5 6 7 P→SL→V→D→Hth→C→D	(mEq./l.)				(mEq./l.)		
		CO_2	Cl	Na	K	Cl	Na	K
S.H. 3	" " " " " " x	21	79	127	5	120	137	24
R.L. 2	" " " " x	19	72	—	—	—	—	—
S.D. 3	" " " " x	30	81	129	4	139	165	24
W.C. 4	" " " " x	29	77	—	—	119	169	15
K.T. 9	" " " " x	—	81	127	3	75	88	—
C.J. 13	" " " " x	30	89	131	5	132	121	16
	Average	26	80	128	4	106	136	19

* Symptoms: 1—perspiration; 2—salt loss; 3—vomiting; 4—dehydration; 5—hyperthermia; 6—coma; 7—death.

† After recovery.

to 118 mg./100 cc. two days after admission, at a time when the fluid balance had been restored. Eventually, however, both central nervous system and kidney function returned to normal.

Four of the six "heat casualties" had virtual absence of respiratory involvement and the other two a relatively minor degree of pulmonary disease. This correlation confirming that of Kessler and Andersen[1] again suggests that the respiratory disease is unimportant in relation to heat casualty.

DISCUSSION

1. Abnormal Electrolyte Composition of Sweat: In view of the results reported in this paper it seems established that the values for sweat chloride and sodium are markedly increased in cystic fibrosis of the pancreas, apparently above those associated generally with other kinds of disease. The same is true of the potassium content of sweat, although not to the same degree.

In the course of these studies it was shown that pancreatic deficiency, chronic pulmonary disease and the administration of several drugs do not *per se* elevate the electrolyte concentration of sweat. In patients with fibrocystic disease of the pancreas the behavior of the kidney following salt restriction and of the adrenal following administration of ACTH, so different from that of patients with nephritis or Addison's disease, excludes these two organs as cause of the high sweat electrolytes in this condition. The dissociation between increased electrolytes in the sweat and the low sodium and chloride levels in the

urine during the periods of low-salt diet appears thus far to be a unique characteristic of cystic fibrosis of the pancreas.

The fact that the sweat glands do not retain salt effectively in hot weather, during salt restriction or when DCA is administered, points to a disturbance in the sweat glands themselves. It is too early to say whether abnormally high electrolytes in the sweat are pathognomonic of fibrocystic disease of the pancreas, but they have come to be an expected finding. The "sweat test" has already proved of assistance in differentiating between cystic fibrosis of the pancreas, familial dysautonomia, celiac disease and certain chronic lung conditions.[12]

In separate studies[13] evidence is being accumulated showing that the parotid secretory rate is abnormally high in patients with fibrocystic disease of the pancreas as compared with controls, and that the sodium and chloride concentration in mixed saliva is likewise elevated. The fact that both the sweat and the salivary glands are affected, as well as the pancreas, the lungs and other organs, re-affirms that one may be dealing with a generalized disease process of which the pancreatic and respiratory components are only one expression, although clinically the most striking manifestation. It also suggests that the secretory activity of many and perhaps all exocrine glands, mucus-producing and others, is disturbed in cystic fibrosis of the pancreas. The term "mucoviscidosis", applied by many to this disease, does not seem justified in view of the fact that at least two nonmucus-secreting structures are affected.

Finally, a preliminary survey of the relatives[13] of patients with this condition indicates that several members of such families have sweat electrolyte concentrations which are distinctly high, although somewhat below the range of patients with the manifest disease.

2. "Heat Casualties" in Cystic Fibrosis of the Pancreas: The levels of sweat chloride and sodium in cystic fibrosis of the pancreas are closely comparable to those in the serum. In view of the fact that the amount of sweating is apparently not decreased, it is evident that through this mechanism the loss of salt in hot weather must be great.

Heat exhaustion[14] in its simplest sense is a physiologic breakdown usually occurring during physical exertion in a hot environment, when vasomotor control and cardiac output are inadequate to meet the need for increased circulation of the skin as well as muscle and brain. Dehydration and salt loss may contribute to the susceptibility to heat exhaustion but are not primary causes. Heat stroke is a failure of adequate heat elimination almost always related to a breakdown of the sweating mechanisms; it may occur whenever heat regulation is dependent on sweating for long periods of time. Its distinguishing characteristic is an extreme elevation of body temperature. Heat prostration is a term sometimes used for severe heat exhaustion or incipient heat stroke.

Neither vascular collapse nor hyperthermia appears to play a primary role in the "heat casualties" of cystic fibrosis of the pancreas. Hyperpyrexia occurs rarely and then is presumably secondary to severe dehydration. In patients with this disease the heat acts only indirectly by precipitating profuse perspiration, which results in a significant loss of sodium-chloride because of the abnormal composition of sweat. The result is a pure salt depletion, a condition which has been clarified experimentally in humans by McCance[15,16] and by the clinical observations of Marriott.[17] Elkinton, Danowski and Winkler[18–20] described the hemodynamic changes in dogs during acute sodium chloride deficit. It was pointed out by these authors, Marriott and others, that a loss of 30% or more of the available sodium chloride produced great reduction in the extracellular fluid resulting in peripheral vascular collapse. There is not much change in the intracellular fluid and by the time

the electrolyte values in the serum decrease, marked reduction in extracellular fluid has occurred. The circulatory changes produced by pure salt depletion are much more severe than those seen in pure water depletion and similar in all ways to the shock following extensive burns, trauma and hemorrhage.

The large experience of Marriott[17] with British troops in India during the last war is of special interest, because the profuse sweating with liberal intake of unsalted water reproduced in normal individuals the situation that takes place in hot weather in patients with cystic fibrosis of the pancreas. In his observations as in those in patients with fibrocystic disease there was a notable absence of heat cramps, which in the light of our present knowledge would appear to be due to salt depletion under rather special conditions perhaps dependent on heavy muscular work. Marriott estimated that when between 0.5 and 0.75 gm. of salt had been lost/kg. body weight, anorexia, nausea and frequently vomiting ensued. The vomiting sets up a vicious circle with further loss of salt and then of water. What starts out as a pure salt depletion becomes then a mixed water and salt depletion, thus increasing the dehydration present as a consequence of salt loss. When more than 0.75 gm. of sodium chloride are lost/kg. body weight peripheral vascular collapse follows, which is the cause of death. In this type of depletion thirst is not a prominent symptom.

These studies suggest that acute salt loss through the sweat should be suspected when patients with fibrocystic disease of the pancreas are admitted during a period of hot weather with vomiting and some dehydration. Thirst is an unreliable symptom. Hyperpyrexia, cardiovascular collapse and at times coma represent a further step in salt depletion and bring about an acute medical emergency. The patient may be in imminent danger of death unless prompt and vigorous measures are undertaken to restore the depleted water and electrolyte stores.

The sequence of events that takes place in hot weather in patients with cystic fibrosis of the pancreas is due in large measure to pure salt depletion with contraction of the extracellular fluid space, a situation which is rapidly reversible with sodium chloride administration.[18] The only solution urgently needed is therefore physiologic saline.

Total serum protein is frequently decreased in acute salt depletion, but probably without loss from the body since it has been shown experimentally[19] that the serum protein level returns to normal when fluids and salt are restored.

Summary

The electrolyte composition of sweat secreted in response to a standard mild thermal stimulus was found to be abnormal in 43 patients with cystic fibrosis of the pancreas. Sodium and chloride concentrations in sweat were 2 to 4 times as high as those found in 50 patients with a variety of other diseases. Sweat potassium levels were also increased in cystic fibrosis of the pancreas although not to the same extent. In contrast, the amount of sweat was not significantly different in patients with fibrocystic disease of the pancreas and control patients.

It was shown that pancreatic deficiency, chronic pulmonary disease and the administration of certain drugs do not *per se* affect the electrolyte composition of sweat. It was also demonstrated by metabolic studies that disturbances in renal and adrenal function are not responsible for the high sweat chloride and sodium in fibrocystic disease. The dissociation between increased electrolytes in the sweat and their very low levels in the urine during salt restriction are unique to this condition.

The fact that the sweat glands do not retain salt effectively in hot weather, during salt restriction or when DCA is administered, points to a disturbance in the sweat glands themselves. This abnormality may not be pathognomonic of cystic fibrosis of the pancreas, but it is an expected finding.

These disturbances in sweat composition together with preliminary observations of abnormal salivary gland secretion suggest that the secretory activity of many and perhaps all exocrine glands is affected in cystic fibrosis of the pancreas. The term "mucoviscidosis" does not seem justified in view of the fact that at least two nonmucus-secreting structures are affected in this condition.

Massive salt loss through sweating in hot weather accounts satisfactorily for the "heat casualties" in cystic fibrosis of the pancreas. The mechanisms are discussed and it is emphasized that the symptoms are initiated by pure salt loss and the consequent reduction in extracellular fluid volume. Since the condition may, if not treated, lead to fatal cardiovascular collapse, it should be regarded as an acute medical emergency.

Under the usual circumstances, serum electrolyte concentrations are normal in fibrocystic disease of the pancreas. In the presence of marked pulmonary dysfunction in this disease, the bicarbonate of the plasma is elevated and the chloride reduced in compensation. It is therefore necessary to demonstrate a lowered serum sodium as well as chloride to detect the massive salt loss which may occur in hot weather.

Acknowledgment

The authors wish to express their gratitude for her help to Miss Adelaide E. Vrooman, Babies Hospital Social Service.

References

1. Kessler, W. R., and Andersen, Dorothy H., Heat prostration in fibrocystic disease of pancreas and other conditions, PEDIATRICS **8**:648, 1951.
2. Darling, R. C., di Sant'Agnese, P. A., Perera, G. A., and Andersen, Dorothy H., Electrolyte abnormalities of sweat in fibrocystic disease of pancreas, Am. J. M. Sc. **225**:67, 1953.
3. Darling, R. C., Some factors regulating composition and formation of human sweat, Arch. Phys. Med. **29**:150,1948.
4. Keys, A., Microdetermination of chlorides in biological materials, J. Biol. Chem. **119**:245, 1936.
5. Johnson, R. E., Pitts, G. C., and Consolazio, F. C., Factors influencing chloride concentration in human sweat, Am. J. Phys. **141**:575, 1944.
6. Wiener, J. S., Regional distribution of sweating, J. Physiol. **104**:32, 1945.
7. Kuno, Y., Physiology of Human Perspiration, London, J. & A. Churchill, Ltd., 1934.
8. Ladell, W. S. S., Thermal sweating, Brit. M. Bull. **3**:175, 1945.
9. Harrison, H. E., Finberg, L., and Fleishman, E., Disturbances of ionic equilibrium of intracellular and extracellular eletrolytes in patients with tuberculous meningitis, J. Clin. Investigation **31**:300, 1952.
10. Conn, J. W., Electrolyte composition of sweat, Arch. Int. Med. **83**:416, 1949.
11. Perera, G. A., and Blood, B. W. Disturbance in salt and water metabolism in hypertension, Am. J. Med. **1**:602, 1946.
12. di Sant'Agnese, P. A., Grossman, H., and Shea, E., Properties of saliva and observations on electrolyte composition of gastric and duodenal contents in cystic fibrosis of pancreas, to be published.
13. di Sant'Agnese, P. A., Darling, R. C., Perera, G. A., and Shea, E., Sweat electrolyte disturbances associated with childhood pancreatic disease, Am. J. Med. **15**:777, 1953.
14. Darling R. C., in Cecil, R. L., and Loeb, R. F., Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1951, p. 500.
15. McCance, R. A., Experimental sodium chloride deficiency in man, Proc. Roy. Soc. (Series B) **119**:245, 1936.

16. McCance, R. A., Medical problems in mineral metabolism. III. Experimental human salt deficiency, Lancet **1**:823, 1936.
17. Marriott, H. L., Water and Salt Depletion, American Lectures in Physiology, Springfield, Ill., Charles C Thomas, Publisher, 1950.
18. Elkinton J. R., Danowski, T. S., and Winkler, A. W., Hemodynamic changes in salt depletion and in dehydration, J. Clin. Investigation **25**:120, 1946.
19. Danowski, T. S., Winkler, A. W., and Elkinton, J. R., Treatment of shock due to salt depletion, comparison of hemodynamic effects of isotonic saline, hypertonic saline and isotonic glucose solution, J. Clin. Investigation **25**:130, 1946.
20. Elkinton, J. R., Winkler, A. W, and Danowski, T. S., Importance of volume and tonicity of body fluids in electrolyte shock, J. Clin. Investigation **26**:1002, 1947.

SPANISH ABSTRACT

Composición Electrolítica Anormal del Sudor en la Fibrosis Quística del Páncreas

Durante el mes de agosto de 1948, con motivo del intenso calor sufrido en la ciudad de Nueva York, se observó que 5 de cada 10 niños ingresados al Babies Hospital, padecían fibrosis quística del páncreas. Kessler y Andersen han señalado que tales pacientes responden adversamente a las ondas cálidas sin precisar el mecanismo responsable de esta conducta. Los presentes autores basándose en que en la fibrosis quística del páncreas puede haber un trastorno pluriglandular incluyendo las glándulas sudoríficas, decidieron hacer un trabajo que incluyera tanto el estudio de la composición electrolítica y la cantidad de sudor en pacientes con este padecimiento como el análisis de los hallazgos en relación al cuadro clínico durante los períodos de calor y a la fisiología patológica de la enfermedad.

Dos grupos fueron observados: 43 casos con fibrosis quística del páncreas, con edad variable de 2 a 16 años de edad, y 50 casos control (40 niños de 1½ a 16 años y 10 adultos de 35 a 62 años de edad). Se señalan los métodos de trabajo.

La composición electrolítica del sudor, obtenido en repuesta a una excitación térmica, fue anormal en los 43 pacientes del primer grupo; su contenido en sodio y cloruros fue de 2 a 4 veces mayor, y en potasio más elevado aunque no en el mismo grado, que en los 50 casos control. Por el contrario, la cantidad de sudor fue semejante en ambos grupos. Se observó que ni la deficiencia pancréatica, ni el proceso pulmonar crónico, ni la administración de ciertas drogas, afectaron por sí mismos la composición electrolítica del sudor; tampoco que los trastornos en las funciones renal y suprarrenal determinaran el exceso de contenido de cloruros y sodio del sudor en los pacientes con fibrosis quística.

La falta de retención de sal durante los períodos calurosos o cuando se restringe la misma, o bien cuando se administra acetato de desoxicorticosterona, hace pensar que el trastorno radica en las mismas glándulas sudoríficas, anormalidad que sin ser patognomónica de la fibrosis quística del páncreas, confirma la sospecha de que existen trastornos pluriglandulares, incluyendo las glándulas salivales y otras exócrinas.

La pérdida masiva de sal por la sudoración durante el verano y períodos calurosos explicaría los accidentes por calor en las fibrosis quísticas del páncreas, que pueden llevar a un colapso cardiovascular fatal si no se les trata; esta depleción salina acentuada es rápidamente reversible si se aplica suero fisiológico oportunamente.

Las concentraciones electrolíticas del suero en la fibrosis quística del páncreas son normales bajo condiciones normales; al agregarse un cuadro de disfunción pulmonar marcada se eleva el bicarbonato plasmático y como compensación se reducen los cloruros.

622 West 168th Street

CLOT DENSITY METHOD OF FIBRINOGEN DETERMINATION IN SOME PEDIATRIC CONDITIONS

By ABRAM KANOF, M.D., SAMUEL LOSNER, M.D., AND BRUNO W. VOLK, M.D.
Brooklyn

THE fibrinogen concentration of the plasma is increasingly recognized as an index of inflammation. Fahraeus demonstrated the predominant influence of the fibrinogen upon the sedimentation rate and showed that the suspension stability of the blood varies inversely with the concentration of that protein.[1] Subsequent studies have revealed, however, that many other factors also affect the sedimentation rate. Among these are the various globulins,[2–4] the cholesterol,[5] the viscosity of the plasma[1, 2] and the size of the red blood cells[1, 2] as well as their electrostatic charge.[2] In recent studies the course of some inflammatory diseases has been followed by direct chemical determinations of the fibrinogen and the results have been compared with the sedimentation rate.[6–9] However, chemical determination of fibrinogen is too elaborate and time-consuming to allow for frequent use as a clinical aid Moreover, the chemical procedure which uses precipitation as a primary step produces inaccuracies since globulins close to fibrinogen are also carried down. These two objections were overcome when two of the authors (S.L. and B.W.V.) reported a rapid and simple method of fibrinogen determination based upon the increasing optical density of coagulating plasma which has been termed the clot density method.[10, 11]

This rapid method, employing relatively small amounts of blood, and capable of being performed within a few minutes seems particularly useful in pediatric practice. The authors therefore undertook a study to evaluate the fibrinogen levels in inflammatory processes as obtained with this technic, and compared the results with the corrected sedimentation rate.

METHODS

A. Clot density: Venous blood was withdrawn and added in a ratio of 9 to 1 to 0.1 molar solution of sodium citrate. After centrifugation, 0.1 cc. of plasma and 0.1 cc. fresh rabbit brain thromboplastin (Difco) were placed in a cuvette measuring 6 mm. in diameter and 7.5 cm. in length. This mixture was then incubated in a water bath at 37° for 3 min. Thereafter, the cuvette was placed into the microadapter of a Coleman Junior Spectrophotometer Model 6A with the wavelength set at 500 mμ and 0.1 cc. of 0.02 molar solution of calcium chloride was blown swiftly into the cuvette. At this point, the optical density was read from the (upper) optical density scale and recorded. At the instant of clotting the galvanometer light beam suddenly began to move to the left. The final optical density was read and recorded and the first value was subtracted from the second reading. The difference, multiplied by 100, was termed "clot density." From this value the fibrinogen level was calculated according to the following formula:

$$F = 18d + 120,$$

F indicating fibrinogen in mg./100 cc. plasma and d representing the clot density. The clot density in normal individuals of either sex ranges from 5 to 15.

B. Sedimentation rate: The corrected sedimentation rate was determined according to Wintrobe's mention.[12]

From the Department of Pediatrics and the Division of Laboratories, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn.

(Received for publication March 13, 1953.)

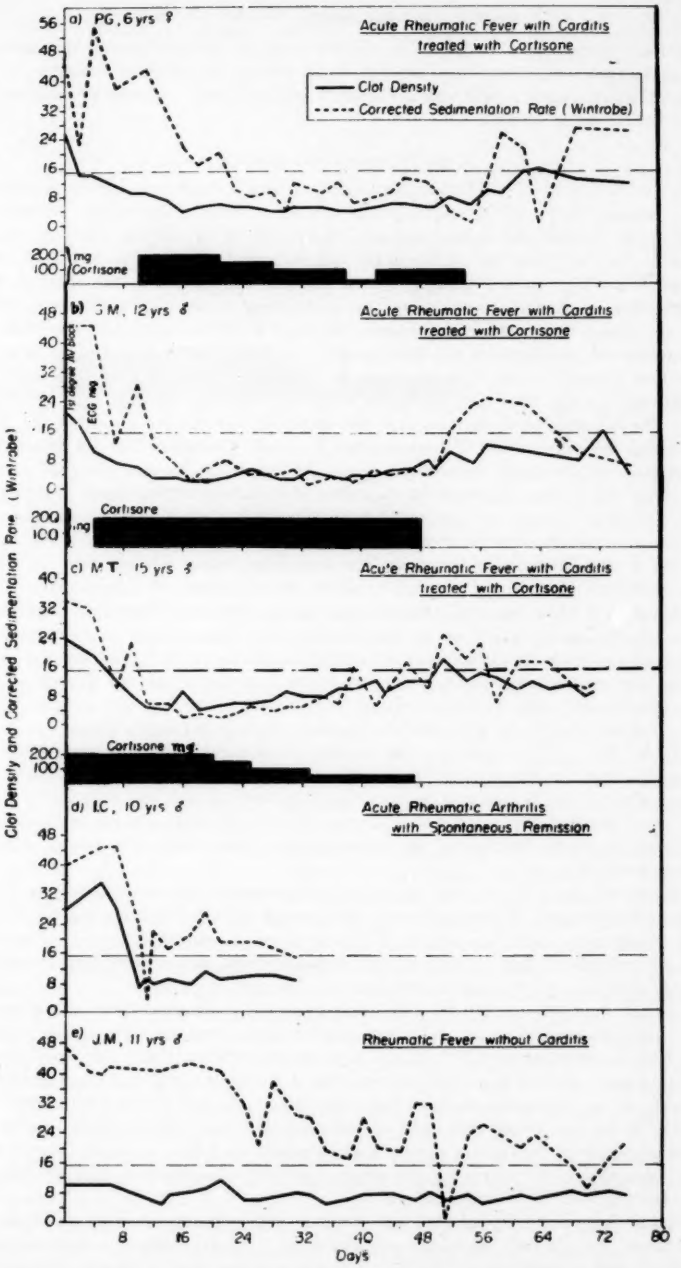


CHART 1. Comparative course of clot density and corrected sedimentation rate in 5 patients with acute rheumatic fever.

Material

Twenty-four children were studied. This number included 11 children with rheumatic fever, 2 children with upper respiratory infections, 1 child with a genitourinary infection, 2 children with fever of central origin, 1 child with a pulmonary infarction and 7 children who suffered no acute illness and who served as controls.

Case Histories and Results

Case 1 (P. G.), a 6 yr. old female, was admitted with a diagnosis of acute rheumatic fever. She had a similar attack 1 yr. previously, but developed no murmur until 4 mo. before admission. On entering the hospital the patient appeared moderately ill. There was swelling, redness and tenderness of the right knee and of the distal interphalangeal joints of the left hand. Heart size was normal but a high pitched blowing systolic murmur was audible at the apex, as well as a decrescendo blowing diastolic murmur over the aortic area, transmitted to the apex. Spleen was palpable 1½ fingers below the costal margin. Repeated ECGs were normal. The child received cortisone which was instituted on the 10th hospital day. The various daily dosages were 200 mg. from the 10th to the 21st day, 150 mg. from the 22nd to the 28th day, 100 mg. from the 29th to the 38th day, 25 mg. from the 39th to the 42nd day and again 100 mg. from the 43rd to the 54th day. The corrected sedimentation rate was markedly elevated on admission and spiked erratically during the entire period of treatment and for 6 wk. thereafter. The clot density was moderately elevated on admission, returned to normal by the third day and remained normal from then on except for 1 minor elevation 10 days after cortisone was discontinued (chart 1a).

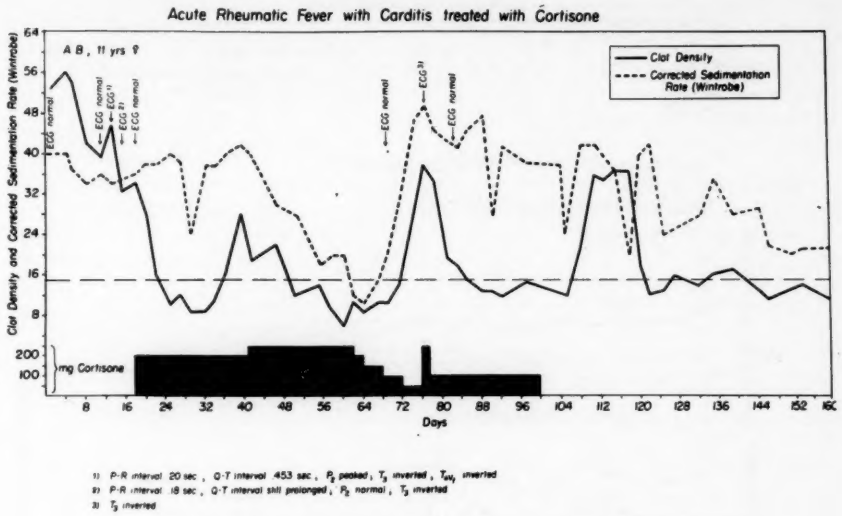
Case 2 (G. M.), a 12 yr. old boy, was admitted in his first attack of rheumatic fever. He was acutely ill on admission with fever and multiple joint pains. ECG revealed a P-R interval of .28 sec. and a ventricular rate of 125/min. The sedimentation rate was high but the clot density was only moderately elevated and returned to normal on the second day (chart 1b) at which time the first degree A-V block had also subsided. This period of electrocardiographic improvement was very well reflected in the course of the clot density. The sedimentation rate, however, failed to reflect this improvement. When cortisone was instituted, there was a further decrease of the clot density, but the sedimentation rate spiked to 29 before returning to normal. Patient made an uneventful recovery after discontinuing cortisone. Sedimentation rate, however, rose to 25 and remained at that level for 1 wk. while the clot density stayed normal throughout.

Case 3 (M. T.), a 15 yr. old boy, was admitted about 6 wk. after the onset of an attack of acute rheumatic fever, characterized by fever and arthralgia. On admission he had a systolic murmur at the apex. On the 5th hospital day he was placed on cortisone 200 mg. daily and this dose was continued until the 21st day, when it was increased to 250 mg. daily. On the 26th day it was decreased to 100 mg. daily. On the 33rd day the dosage was further reduced to 50 mg. daily and was discontinued on the 47th day.

The comparative study of the clot density and sedimentation rate was begun only 2 wk. after admission. Administration of cortisone which was started the day following the initiation of the study was promptly followed by a decline of the clot density to normal (chart 1c). The sedimentation rate followed in a parallel fashion. After discontinuance of cortisone both the clot density and the sedimentation rate rose moderately but returned promptly to normal.

Case 4 (I. C.), a 10½ yr. old boy, had his first attack of rheumatic fever 9 mo. prior to admission. This episode lasted 3 mo. and subsided while under treatment with cortisone. He was readmitted with a temperature of 38.8°C. and pain in the right shoulder. The fever persisted for 8 days during which time he also complained of pain in the left shoulder. His heart appeared normal on admission but a soft systolic murmur became audible at the apex on the 13th hospital day. His spleen was felt on the 5th day and remained enlarged until discharge. Both the clot density and sedimentation rate were elevated on admission and continued to follow a parallel course (chart 1d). With the subsidence of the fever, the clot density reached normal and remained so while the sedimentation rate continued to fluctuate temporarily.

Case 5 (A. B.), an 11 yr. old girl, was admitted with a history of acute rheumatic fever of 3 mo.' duration. She had had "growing pains" for about 1 yr. previously. On admission the patient was acutely ill with a temperature of 40.0°C., a systolic murmur grade 3, a tender abdomen throughout, and painful joints in all extremities. The generalized arthralgia became worse during the 1st week, but improved thereafter. On the 8th day her spleen became palpable. The clot density on


Acute Rheumatic Fever with Carditis treated with Cortisone
A B , 11 yrs ♀
Clot Density
Corrected Sedimentation Rate (Wintrobe)
Clot Density and Corrected Sedimentation Rate (Wintrobe)
mg Cortisone
Days

1) P-R interval 20 sec , Q-T interval 453 sec , P_2 peaked , T_2 inverted , T_{aV_1} inverted
2) P-R interval 18 sec , Q-T interval still prolonged , P_2 normal , T_2 inverted
3) T_2 inverted

CHART 2. Comparative course of clot density and corrected sedimentation rate in patient with severe acute rheumatic fever treated with cortisone.

admission was 56 (chart 2), the highest value seen in this series, and started to recede on the 4th day. The sedimentation rate, however, was at the same general level as seen in most cases of rheumatic fever and remained elevated. Cortisone, 200 mg./day, was started on the 19th day. There was a prompt fall of the clot density to normal, while the sedimentation rate remained unchanged. On the 39th day the clot density began to rise. Concomitantly, there was a temperature elevation and a recurrence of the clinical symptoms. The dosage of cortisone was then increased to 250 mg. daily. The clot density again returned to normal and this time the sedimentation rate also began to decline. When both the clot density and the sedimentation rate were well within normal limits cortisone was gradually decreased to 50 mg./day. There was an immediate exacerbation of all symptoms as well as an increase in the sedimentation rate and clot density. At the height of the exacerbation cortisone 250 mg. daily were instituted. There was an immediate improvement of the clinical condition. The clot density again declined steeply within the following 7 days, whereas the sedimentation rate remained elevated for the following 3 mo., the remainder of the hospital stay. Three and a half weeks after the last exacerbation cortisone was discontinued causing again a flare-up of symptoms and a rise in the clot density. The sedimentation rate which had been elevated did not reflect this "rebound." Symptoms receded within a week as did the clot density.

The child was well at discharge at the end of 3 mo. The clot density was normal except for a slight increase during an upper respiratory infection; the sedimentation rate never fell below 20.

Case 6 (J. M.), an 11 yr. old boy, was admitted with a history, 3 wk. in duration, of widespread joint pains. During his 3 mo. stay the child manifested pains in some of his large joints but most of his disability was in the small joints of the hands, feet and spine. Intensive clinical and laboratory studies revealed no evidence of cardiac involvement, and he was discharged with the diagnosis of rheumatic fever without carditis. The sedimentation rate fluctuated at high levels, whereas the clot density more accurately mirrored the benign course without therapy (chart 1e). The child was seen in the clinic 6 mo. after discharge. His heart was still normal but the sedimentation rate was elevated to 28.

Cases 7 (J. T.), 8 (F. M.), 9 (J. W.), 10 (G. R.), 11 (P. R.) are patients who were included in this study after they had completely recovered from an attack of rheumatic fever. Chart 3 illustrates the stability of the clot density once it has reached a normal level. The sedimentation rate, however, remained constantly elevated in 1 of the 5 patients, while in the other 4 it displayed considerable fluctuations.

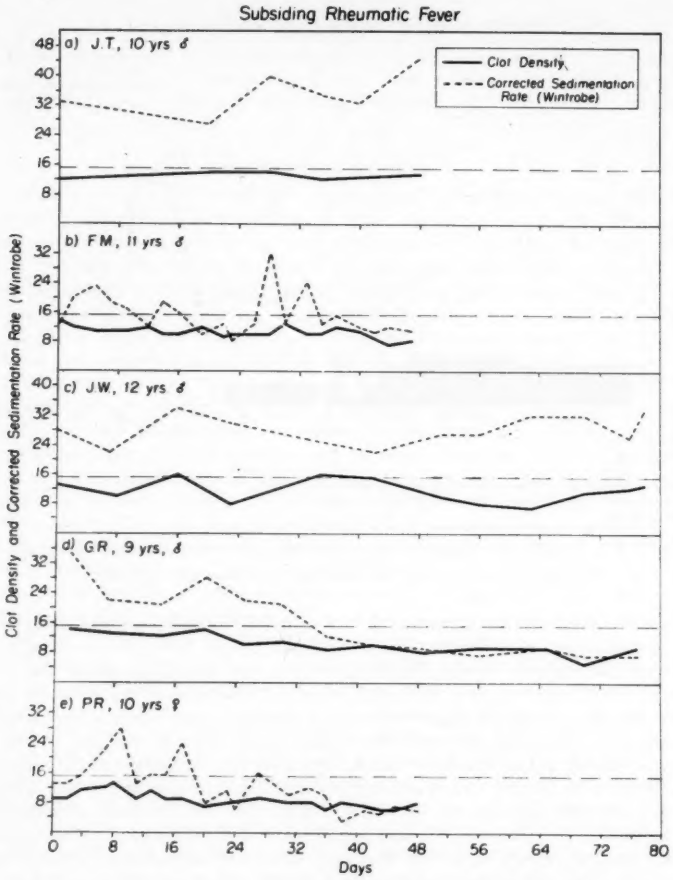

Subsiding Rheumatic Fever
a) J.T, 10 yrs ♂
Clot Density
Corrected Sedimentation Rate (Wintrobe)
b) F.M, 11 yrs ♂
c) J.W, 12 yrs ♂
d) G.R, 9 yrs, ♂
e) P.R, 10 yrs ♀
Clot Density and Corrected Sedimentation Rate (Wintrobe)
Days

CHART 3. Comparative course of clot density and corrected sedimentation rate in 5 cases of subsiding rheumatic fever.

Case 12 (P. M.), a 13 yr. old boy with cerebral palsy, had, during a 2 mo. period, 2 episodes of upper respiratory infection with fever up to 38.8°C. While the sedimentation rate was almost always elevated during this time of observation the clot density rose only moderately during his second upper respiratory infection (chart 4a).

Case 13 (J. T.), a 4 yr. old boy, was admitted with the diagnosis of rheumatic fever. Physical examination on admission revealed a grade 2 systolic murmur. However, extensive clinical, electrocardiographic and laboratory studies failed to confirm the admission diagnosis. The child was discharged with the diagnosis of fever of unknown origin and a functional systolic murmur.

During this period the temperature fluctuated around 38.3°C. The sedimentation rate was equally variable, but the clot density remained normal throughout (chart 3a).

Case 14 (E. B.), a 9 yr. old boy, with spina bifida and meningocele suffered from a low-grade urinary infection. The sedimentation rate was irregularly elevated throughout the period of observation (chart 4b). During the second month there was an increase of urinary symptoms associated with an elevation of the temperature to 38.0°C. for a single day. At this point the clot density rose for the first time and returned to normal within 1 wk.

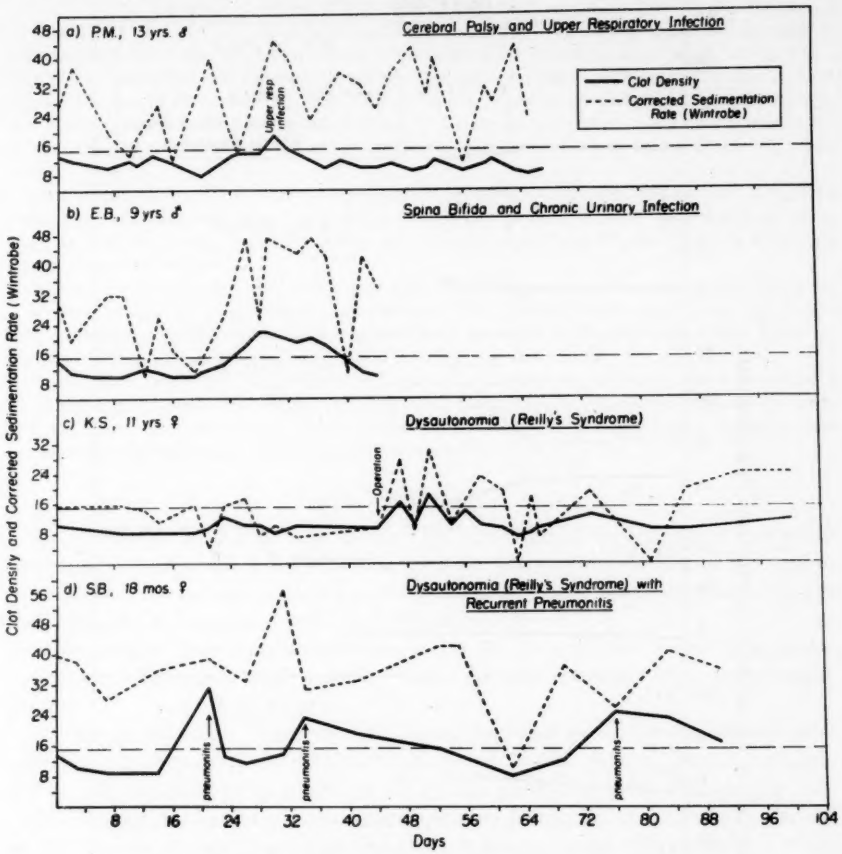

a) P.M., 13 yrs. ♂
Cerebral Palsy and Upper Respiratory Infection
Clot Density
Corrected Sedimentation Rate (Wintrobe)
Upper resp. infection
b) E.B., 9 yrs. ♂
Spina Bifida and Chronic Urinary Infection
c) K.S., 11 yrs. ♀
Dysautonomia (Reilly's Syndrome)
Operation
d) S.B., 18 mos. ♀
Dysautonomia (Reilly's Syndrome) with Recurrent Pneumonitis
pneumonitis
Clot Density and Corrected Sedimentation Rate (Wintrobe)
Days

CHART 4. Comparative course of clot density and corrected sedimentation rate in 2 cases of mild infections and 2 cases of dysautonomia.

Case 15 (K. S.), an 11 yr. old Jewish girl, was admitted with a long standing history of frequent bouts of unexplained fever. At the age of 8 yr. a systolic hypertension and a cardiac murmur were discovered. Extensive study led to the diagnosis of dysautonomia (Reilly's syndrome). During her stay at the hospital she was subjected to an exploration for suspected pheochromocytoma which was not found. The sedimentation rate was frequently elevated while the clot density was always normal (chart 4c). Of special interest is the finding that postoperatively the sedimentation rate rose to 41 mm./hr. while the clot density increased but slightly above normal. The clinical course was uneventful.

Case 16 (S. B.), an 18 mo. old Jewish girl, was admitted with all the clinical findings of dysautonomia (Reilly's syndrome). In her case a disturbing factor was her tendency to run a high fever up to 41.6°C. without other clinical findings. However, during the third week of her hospital stay she developed a definite pneumonia, confirmed roentgenologically.

During the early period of unexplained fever, the sedimentation rate was considerably elevated while the clot density remained normal (chart 4d). When the child developed pneumonia the clot density rose sharply, and fell to normal when the pneumonic process resolved. The sedimentation rate continued elevated. In an exacerbation of the pneumonitis clot density again increased temporarily.

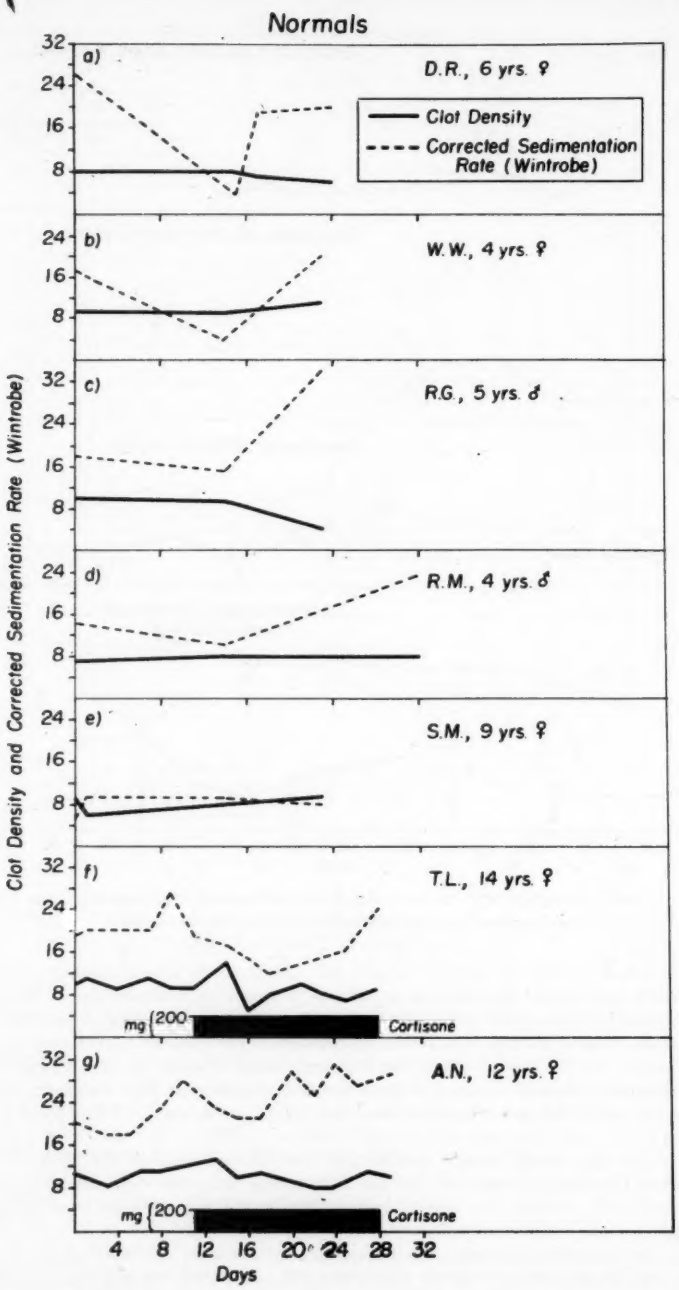


CHART 5. Comparative course of clot density and corrected sedimentation rate in 7 normal control cases, 2 of whom were given cortisone 200 mg. daily for 17 days each.

Case 17 (L. S.), a 7 yr. old girl, was admitted critically ill in cardiac decompensation due to Lutembacher's syndrome. She had a normal temperature for a period of about 6 mo. during which time her sedimentation rate and clot density were followed and found to be constantly normal. During her 6th month of hospital stay, the child developed a pulmonary infarction. Both clot density and sedimentation rate rose precipitously. The clot density declined to normal within 1 wk. as the pulmonary condition improved but the sedimentation rate remained irregularly elevated for about 2 mo.

In a control study of 7 normal children the sedimentation rate and clot density were determined serially over a period of at least 3 wk. (chart 5). The clot density remained normal without variations. In 1 of the 7 cases, the sedimentation rate behaved similarly; in all other instances there were elevations to abnormal levels.

In order to observe the effect of cortisone upon the fibrinogen concentration in normal children, 2 of these controls in whom both the sedimentation rate and clot density were studied for 1 wk., were subsequently given cortisone 200 mg. daily for a period of 3 wk. The authors were unable to find any changes in the fibrinogen concentration resulting from this procedure.

These results were then corroborated by experiments carried out in 4 dogs over a period of 4 wk. Two dogs received each cortisone 50 mg. daily while the other 2 animals received cortisone 100 mg. daily. The clot density was determined every other day and showed no deviation from normal values throughout the entire period of observation.

Discussion

The cases reported in this study illustrate the advantages of the clot density method of fibrinogen determination in the evaluation of acute inflammation. The use of this method in serial studies produces a smooth curve without the erratic fluctuations so frequently seen when the sedimentation rate is followed similarly.

In the authors' experience an elevation of the clot density above normal is associated with active inflammation while a decline always indicates a decrease of the inflammatory process.

In cases of rheumatic fever observed during the acute phase, the clot density curve smoothly and promptly followed the clinical course. In two patients (chart 1a and 1b), the clot density declined to normal as the clinical picture improved although the sedimentation rate continued to fluctuate above normal. In another case (chart 2), the clot density was the highest observed in this study, a fact in accord with her critical condition on admission as well as with her clinical course which was more prolonged than in any of the patients included in this study. The initial phase was characterized by a limited improvement of the clinical picture not reflected in the sedimentation rate but accurately mirrored by the slowly receding clot density.

In two patients (charts 1b and 2) there was also correlation between clot density and electrocardiographic changes, a feature not displayed by the sedimentation rate.

In the present study cortisone was usually withdrawn when both the sedimentation rate and the clot density had returned to normal. This was followed in all instances by a worsening of both the clinical and the laboratory findings. Whereas this "rebound" was followed by a prolonged elevation of the sedimentation rate for several weeks or months (chart 2), the clot density rather rapidly returned to normal presaging the subsidence of the "rebound."

In five cases (chart 3), serial determination of the sedimentation rate and clot density were begun after complete subsidence of a cycle of rheumatic fever. The clot density in all five remained flat during this period of convalescence whereas the sedimentation rate stayed elevated in some and showed erratic fluctuations in others.

The two cases of dysautonomia (charts 4c and 4d) suggest that fever of central origin

may be accompanied by elevation of the sedimentation rate; the clot density, however, remains normal as long as there is no inflammatory process.

The discriminatory feature of the clot density is illustrated in two of the patients (charts 4a and 4b). In each of these the clot density rose moderately with mild infections and declined promptly when the infection was brought under control. The sedimentation rate, however, was elevated throughout and during the period of mild infection rose to heights seen in the severe cases of rheumatic fever.

The results in normal controls show that the clot density in contrast to the sedimentation rate does not display fluctuations beyond the normal level.

Fearnley and Bunim[13] reported that the administration of corticotropin reduces the fibrinogen concentration of normal individuals in a nonspecific manner. The present authors' results in normal children after administration of cortisone as well as those obtained in dogs strongly suggest that cortisone is devoid of any nonspecific effect upon the fibrinogen concentration. The authors therefore believe that the reduction of the fibrinogen concentration following the administration of cortisone in rheumatic fever is caused by the depression of the inflammatory process itself.

The diagnostic tests for rheumatic fever can be classified into two groups, one of semispecific tests indicating antibody formation against group A streptococci and another group of nonspecific tests indicative of the degree of inflammatory activity, once the diagnosis has been established. Among the latter, the sedimentation rate has attained prominence because of its relative simplicity and lack of dependence on special reagents. While it is recognized that the fibrinogen concentration of the plasma is the major factor in determining the degree of settling of the red blood cells, its determination has encountered technical difficulties which the authors believe have been overcome in the clot density method.

In rheumatoid arthritis the correlation between sedimentation rate and fibrinogen has been found to be close,[6,7] although it is conceded that the fibrinogen concentration reflects more accurately the intensity of the disease. In rheumatic fever there has been no detailed serial study of the fibrinogen concentration, sedimentation rate, degree of activity and their response to cortisone therapy. The study suggests that the clot density method of fibrinogen determination is practical for evaluating the degree of active inflammation particularly when performed serially. It was found that a normal clot density does not necessarily indicate absence of rheumatic activity. However, an elevated clot density always signifies an active inflammatory process and does not exhibit the erratic elevations observed with the sedimentation rate. Moreover, while the sedimentation rate is rarely discriminatory both because of its erratic behavior and because physicochemical considerations prevent its further rise when the fibrinogen concentration of the plasma exceeds 700 mg./100 cc.,[7] the clot density usually varies directly with the intensity of clinical manifestations.

In the rheumatic fever patients, all of whom were treated with cortisone, the clot density was the first laboratory criterion to recede with clinical improvement. It stayed at normal levels with great consistency and rose promptly when there was a "rebound" after cessation of therapy, and declined quickly when the "rebound" subsided. This latter finding was of particular significance because the sedimentation rate continued at high levels for many weeks following a "rebound" without indicating that inflammatory activity was subsiding.

Summary

The clot density, a method of rapid fibrinogen determination, was studied serially in a group of children and compared simultaneously with the corrected sedimentation rate.

In normal children the clot density showed no deviation from the normal levels which range from 5 to 15, while the sedimentation rate displayed many erratic fluctuations.

In such conditions as upper and lower respiratory infections or urinary tract infections, the clot density rose slightly and subsided promptly under therapy while the sedimentation rate frequently showed maximum elevations.

In acute rheumatic disease, there was constant and close correlation between the degree of clinical manifestations and the clot density. The sedimentation rate, however, frequently did not correspond with the intensity of the inflammatory process.

In rheumatic children treated with cortisone, the clot density is the first indication of a therapeutic effect. Moreover, with the cessation of cortisone administration and the worsening of clinical symptoms as well as laboratory data, the decline of the clot density is the first indication of a "rebound" rather than an exacerbation.

The clot density may be an aid in the differentiation of fever of central origin.

Cortisone seems to be devoid of a direct nonspecific effect upon the fibrinogen concentration.

Acknowledgments

Appreciation is due the Mildred Forman Foundation for their contribution to the maintenance of the rheumatic fever patients. The authors also acknowledge the cooperation of the Department of Cardiovascular Research (Dr. S. R. Slater, Director) as well as the technical assistance of Miss M. Y. Gilady.

References

1. Fahraeus, R., Suspension stability of blood, Acta med. Scandinav. **5**:1, 1921.
2. Thygesen, J. E., Mechanism of blood sedimentation, Acta med. Scandinav. (Supp.) **134**:1, 1942.
3. Alfred-Brown, G. R. P., and Munro, J. M. H., Blood sedimentation rate and plasma proteins, Lancet **1**:1333, 1934.
4. Ropes, M. W., Rossmeisl, E., and Bauer, W., Relationship between erythrocyte sedimentation rate and plasma proteins, J. Clin. Investigation **18**:791, 1939.
5. Kürten, H., Die Senkungsgeschwindigkeit der Roten Blutkörperchen in ihrer Beziehung zu Cholesterin und Lecithin, Arch. f. d. Ges. Physiol. **185**:248, 1920.
6. Vaughan, J. H., Bayles, T. B., and Favour, C. B., Effect of 17-hydroxy-11-dehydrocorticosterone and adrenocorticotropic hormone upon plasma gamma globulin, fibrinogen and erythrocyte sedimentation rate, Proc. Soc. Exper. Biol. & Med. **76**:274, 1951.
7. Fletcher, A. A., Dauphinee, J. A., and Ogryzlo, M. A., Plasma fibrinogen and sedimentation rate in rheumatoid arthritis and their response to administration of cortisone and adrenocorticotropic-hormone (ACTH), J. Clin. Investigation **6**:561, 1952.
8. Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, New York, The Blakiston Company, 1951, pp. 565-568.
9. Bunim, J. J., Kuttner, A. L., Baldwin, J. S., and McEwen, C., Cortisone and corticotropin in rheumatic fever and juvenile rheumatoid arthritis, J.A.M.A. **150**:1273, 1952.
10. Losner, S., Volk, B. W., Jacobi, M., and Newhouse, S., Spectrophotometric studies on clot density, J. Lab. & Clin. Med. **38**:28, 1951.
11. Volk, B. W., Losner, M. D., Jacobi, M., and Lazarus, S. S., Studies on clot density, Am. J. Clin. Path. **22**:99, 1952.
12. Wintrobe, M. M., Clinical Hematology, Philadelphia, Lea & Febiger, 1943, pp. 167-168.
13. Fearnley, G. R., and Bunim, J. J., Effect of ACTH on erythrocyte sedimentation rate and plasma-fibrinogen and serum-protein levels in normal persons, Lancet **2**:1113, 1951.

SPANISH ABSTRACT

La Determinación de Fibrinógeno por el Método de la Densidad del Coágulo

La concentración del fibrinógeno del plasma se ha venido considerando más y más como un índice de estado inflamatorio, desde que Fahraeus demostró la influencia predominante del mismo en la sedimentación globular, entre otros factores. Recientemente se ha estudiado el curso de algunos procesos inflamatorios según la determinación química directa de fibrinógeno, pero siendo ésta de difícil realización, los autores han venido estudiando un método simple y sencillo para determinarlo según la densidad óptica del plasma coagulante, denominándolo método de la densidad del coágulo, con las ventajas de ser rápido, requerir pequeñas cantidades de sangre y ser de aparente utilidad en la práctica pediátrica. En el presente trabajo se hace un estudio de los niveles de fibrinógeno en procesos inflamatorios obtenidos con este método y se comparan con los resultados de la sedimentación globular corregida.

Se estudiaron 24 niños: 11 con fiebre reumática, 2 con proceso infeccioso en las vías respiratorias altas, 1 con infección genitourinaria, 2 con fiebre de origen central, un niño con infarto pulmonar y 7 sin infección aguda que sirvieron como control.

Estos casos mostraron las ventajas para valorizar un proceso inflamatorio, del método de la densidad del coágulo en la determinación del fibrinógeno; su uso en serie da una curva suave, sin las fluctuaciones erráticas tan frecuentemente vistas con determinaciones seriadas de la sedimentación globular. Según la experiencia de los autores el aumento de la densidad del coágulo sobre lo normal indica inflamación activa, y su disminución, atenuación del proceso inflamatorio. Los niños control mostraron una densidad del coágulo con fluctuaciones que no rebasaron los niveles normales (cifras de 5 a 15), en contraste con lo observado en la estudio de la sedimentación globular.

Otros investigadores han encontrado que la administración de cortisona a sujetos normales reduce la concentración del fibrinógeno en forma no específica; nuestros autores piensan en cambio, según sus observaciones, que tal disminución, después de proporcionar cortisona, en los niños control estudiados, en perros y con mayor razón en sus enfermos de fiebre reumática, se debe a acción específica sobre el proceso inflamatorio.

En los niños con infecciones respiratorias y genitourinarias, la densidad del coágulo se elevó ligeramente y descendió pronto con la terapéutica, en tanto que la sedimentación globular presentó elevaciones máximas con frecuencia.

En la fiebre reumática hubo correlación entre la densidad del coágulo y el grado de gravedad de las manifestaciones clínicas; la sedimentación globular no siempre correspondió a la intensidad del proceso inflamatorio. En los niños con fiebre reumática tratados con cortisona, la densidad del coágulo fue la primera en manifestar el efecto terapéutico favorable; se observó además un fenómeno interesante: aumentó al cesar la administración de la droga y declinó posteriormente por sí sola al continuar la mejoría, en tanto que la sedimentación globular persistía elevada durante muchas semanas sin indicar que el proceso inflamatorio iba cediendo.

Los autores creen, por último, que la densidad del coágulo puede ser una ayuda en la diferenciación de la fiebre de origen central pues en estos casos permanece normal ante la ausencia de inflamación.

East 49th Street and Rutland Road

MUCOLYTIC ENZYME SYSTEMS

XX. Comparison of Mucoprotein and Hyaluronidase Inhibitor Concentrations in Maternal and Infant Serum

By ROBERT A. GOOD, M.D., PH.D.,* VINCENT C. KELLEY, M.D., PH.D.,†
THOMAS A. GOOD, M.D.,† AND DAVID GLICK, PH.D.
Minneapolis

RECENT investigations[1,2] have shown that numerous changes occur in the composition of blood during the active stage of many diseases. The substances which vary in concentration under the influence of acute disease have been designated "acute phase reactants".[2] Included in this group are the nonspecific hyaluronidase inhibitor[3,4] and certain acid mucoproteins.[5,6] The serum concentration of each of these latter two constituents is elevated in acute disease and decreases to normal with the subsidence of the activity of the disease process. The clinical usefulness of several of the acute phase reactions, particularly in detecting activity of rheumatic processes has received emphasis,[1,2,6-9] but as yet little is known of the biologic importance of these phenomena. The physiologic role of the reactants and the basis for variations in their serum concentration in disease remain unknown.

Longsworth et al.[10] and others[11,12] have shown that at parturition the protein composition of the serum of mothers differs from that of their infants. Infant serum contains less alpha and beta globulin, relatively more albumin and more gamma globulin than either maternal serum or normal adult serum. Reports that newborn infant serum possesses enhanced bactericidal properties[13,14] against certain micro-organisms suggested the possibility that acute phase proteins, conceivably involved in mechanisms of defense, might be present in different concentrations in the serum of infants than in that of their mothers or of normal adults. As part of a comprehensive study of acute phase reactants and in conjunction with detailed investigations of the protein composition of maternal and infant serum being carried out in these laboratories, a comparison of nonspecific hyaluronidase inhibitor and mucoprotein concentrations in maternal and infant serum was undertaken. It is the purpose of this report to compare mucoprotein and hyaluronidase inhibitor concentration in normal maternal and infant serum at the time of birth, to describe the changes in the serum concentration of these constituents which occur in both maternal and infant blood during the initial postpartum month, and to report the mucoprotein concentrations found in the serum of normal infants at various ages during the first year of life. These data along with those already published from this and other laboratories furnish normal values for mucoprotein concentrations in human serum from birth to old age.

From the Departments of Pediatrics and Physiological Chemistry, University of Minnesota Medical School, Minneapolis.

Aided in part by grants-in-aid from the United States Public Health Service (R.G. 2990 and 974), The Helen Hay Whitney Foundation and the Minnesota Heart Association.

(Received for publication April 30, 1953.)

* Markle Scholar in Medical Sciences.

† Present Address: Department of Pediatrics, College of Medicine, University of Utah, Salt Lake City.

Materials and Methods

The serum specimens, including 33 paired samples of maternal and fetal serum, were obtained in the following manner: 15 to 20 cc. of fetal blood was taken from the placental stump of the umbilical cord immediately after delivery of the baby and prior to separation of the placenta. Maternal blood was drawn from the antecubital vein. Venous blood from infants under 1 yr. of age was taken from the internal jugular vein while samples from children 1 to 15 yr. of age were drawn from the antecubital vein. All blood specimens were placed in clean sterile test tubes, refrigerated at 4° C. for approximately 1 hr. while clotting occurred and centrifuged at 2000 rpm in an International #1 centrifuge. The serum was then removed from the blood, placed in sterile tubes and frozen in the deep freeze at −30° C. where it was stored in the frozen state until the analyses were carried out. Precautions were taken to avoid exposure of any blood or serum sample to room temperature for longer than a total of 30 min., in this way avoiding loss of the heat-labile hyaluronidase inhibitor prior to its measurement. Mucoproteins were determined according to the method of Winzler as previously modified in this laboratory.[6]

The viscosimetric method previously described[15, 16] was used for estimating the content of non-specific hyaluronidase inhibitor in the serum. The concentration of hyaluronidase inhibitor is expressed as the percentage inhibition of the activity of a standard testicular hyaluronidase solution acting on a standard hyaluronic acid substrate prepared from human umbilical cords. In all instances the fetal and maternal samples were handled in exactly the same fashion and regularly the hyaluronidase inhibitor levels of a group of serums from normal healthy children and adults were determined concurrently with those of the experimental group to permit comparison of the infant and maternal samples both with each other and with those of healthy children and adults.

Results

The results of the studies of mucoprotein concentration in the several groups of serum are reported in table 1. Here it will be seen that maternal and infant serum differ from each other in their mucoprotein concentration and that both groups differ significantly from either healthy children or adults. At the time of parturition the mucoprotein concen-

TABLE 1

Mucoprotein Levels in Maternal and Infant Serum

Group	No. Cases	Mean Mucoprotein-tyrosine mg./100 cc.	Range	Standard Deviation	Standard Error of Mean
Newborn Infants (cord blood)	33	1.33	1.05 to 2.70	0.44	0.076
Maternal Blood 1 hr. postpartum	33	3.62	2.10 to 8.45	1.33	0.197
Infants 5–11 days of age (jugular)	17	1.74	1.21 to 2.32	0.70	0.170
Maternal Blood 5–11 days postpartum	20	5.04	2.44 to 9.75	0.60	0.133
Infants 12–30 days of age (jugular)	11	1.90	1.33 to 3.10	0.50	0.15
Maternal Blood 12–30 days postpartum	4	5.13	4.35 to 7.02	—	—
Normal Children 1–12 mo. (jugular)	17	2.85	1.90 to 4.40	0.58	0.11
Normal Children 1–15 yr.	75	2.49	1.9 to 4.5	0.52	0.06
Normal Adults 18–48 yr.	50	2.34	1.9 to 4.3	0.35	0.05

TABLE 2

COMPARISON OF MUCOPROTEIN LEVELS IN MATERNAL AND INFANT SERUMS

Maternal Serum*		Infant Serum†		Difference (Maternal-Infant)
Patient	Mucoprotein Tyrosine mg./100 cc.	Patient	Mucoprotein Tyrosine mg./100 cc.	Mucoprotein Tyrosine mg./100 cc.
Mrs. D.	2.35	Baby boy D.	1.05	1.30
" W.	2.30	" " W.	1.25	1.05
" R.F.	3.95	" " F.	1.25	2.70
" A.	5.30	" girl A.	1.25	4.05
" T.M.	4.45	" " M.	1.25	3.20
" M.	4.45	" " M.	1.25	3.20
" H.	2.50	" boy H.	1.45	1.05
" J.H.	3.85	" " H.	1.30	2.55
" M.A.	2.75	" girl A.	1.30	1.45
" B.	4.65	" boy B.	1.80	2.85
" C.	2.60	" " C.	2.00	0.66
" K.A.	2.70	" " A.	1.20	1.50
" S.A.	3.00	" " A.	1.20	1.80
" D.C.	2.10	" girl C.	1.20	0.90
" O.	3.00	" boy O.	1.15	1.85
" D.D.	3.15	" " D.	1.45	1.70
" R.K.	4.00	" girl K.	2.00	2.00
" H.M.	2.90	" " M.	1.05	1.85
" E.R.	3.65	" boy R.	1.50	2.15
" C.S.	3.65	" girl S.	1.30	2.35
" D.J.	4.20	" boy J.	1.45	2.75
" H.R.	3.45	" " R.	1.15	2.30
" P.R.	4.65	" girl R.	2.15	2.50
" M.R.	8.45	" boy R.	1.70	6.75
" D.K.	4.60	" " K.	1.10	3.50
" E.W.	3.75	" " W.	1.15	2.60
" A.A.	2.90	" " A.	1.50	1.40
" M.H.	2.55	" " H.	2.16	0.39
" R.K.	4.00	" girl K.	2.00	2.00
" L.	3.60	" boy L.	2.70	0.90
" N.	3.76	" girl N.	1.50	2.26
" Z.	3.76	" " Z.	1.50	2.26
Mean	3.65		1.48	2.18
S.E.M.	0.21		0.07	0.21

* Blood drawn from antecubital vein within 1 hr. postpartum.

† Blood obtained from placental stump of umbilical cord after delivery of baby and prior to separation of placenta.

tration of maternal serum is elevated and the level of this serum protein increases in the postpartum period. To the contrary the level of mucoprotein is significantly decreased in the fetal serum samples taken from cord blood immediately after birth. Comparison of the mucoprotein concentration in this group and that of the maternal samples taken within one hour of delivery reveals a rather marked difference (table 1). Only the highest levels in the cord blood samples overlap the lowest levels found in maternal serum.

In table 2 the mucoprotein level of each maternal serum is compared to the level found

TABLE 3

SERUM MUCOPROTEIN CONCENTRATION IN HEALTHY CHILDREN

Pt.	Age	Sex	Muco-protein Tyrosine mg./100 cc.	Pt.	Age	Sex	Muco-protein Tyrosine mg./100 cc.	Pt.	Age	Sex	Muco-protein Tyrosine mg./100 cc.
1. Baby D.	Birth	M	1.05	26. Baby C.	11 day	M	2.40	51. Baby TL.	8 mo.	M	2.00
2. " W.	"	M	1.25	27. " W.	11 "	M	1.60	52. " MG.	9 "	M	2.60
3. " F.	"	M	1.25	28. " C.	14 "	F	1.40	53. " DD.	10 "	M	3.10
4. " A.	"	F	1.25	29. " H.	14 "	M	3.10	54. " AL.	10 "	F	1.90
5. " M.	"	F	1.25	30. " A.	18 "	M	1.80	55. " RN.	10 "	M	2.40
6. " H.	"	M	1.25	31. " N.	18 "	F	1.55	56. " TA.	10 "	F	2.10
7. " O.	"	M	1.25	32. " G.	19 "	M	2.00	57. " JP.	11 "	M	4.40
8. " H.	"	M	1.45	33. " R.	26 "	F	1.55	58. " TC.	12 "	F	3.10
9. " A.	"	F	1.30	34. " L.	27 "	M	1.50	59. " KS.	2 yr.	M	2.70
10. " B.	"	M	1.80	35. " N.	27 "	F	1.60	60. " RG.	2 "	M	2.10
11. " M.	5 day	F	1.35	36. " A.	30 "	F	2.33	61. " ES.	4 "	M	3.30
12. " F.	6 "	M	1.48	37. " LM.	1 mo.	M	2.50	62. " EL.	5 "	M	3.00
13. " M.	6 "	F	1.24	38. " RP.	1 "	F	3.50	63. " RA.	5 "	F	2.60
14. " D.	6 "	F	1.35	39. " AT.	2 "	F	2.65	64. " FC.	5 "	M	2.10
15. " C.	6 "	F	1.49	40. " RJ.	3 "	M	3.70	65. " CA.	6 "	M	3.55
16. " A.	7 "	F	1.68	41. " LD.	3 "	F	3.80	66. " KA.	6 "	F	3.20
17. " M.	7 "	F	2.32	42. " GS.	3 "	F	2.90	67. " JH.	7 "	M	3.50
18. " A.	7 "	M	1.33	43. " JE.	4 "	F	2.50	68. " KS.	8 "	F	3.05
19. " S.	7 "	M	1.50	44. " LB.	4 "	F	2.60	69. " DM.	8 "	M	2.60
20. " N.	7 "	M	1.50	45. " ML.	4 "	M	4.00	70. " SW.	10 "	F	3.20
21. " W.	8 "	F	1.35	46. " GM.	5 "	M	2.75	71. " HB.	12 "	M	3.20
22. " O.	8 "	M	2.00	47. " BB.	6 "	M	3.00	72. " RH.	12 "	M	2.60
23. " L.	8 "	F	1.49	48. " LB.	7 "	F	2.60	73. " TG.	14 "	F	2.40
24. " S.	8 "	M	1.21	49. " KS.	8 "	M	3.00	74. " AL.	15 "	M	2.75
25. " A.	11 "	F	1.55	50. " AT.	8 "	M	2.10				

in the cord blood of the patient's own infant. Without a single exception the value for the fetal serum is lower than that of the maternal serum, a highly significant distribution. The data in this table also suggest that the levels of mucoproteins in the infants' serums are not directly correlated with the levels in the respective maternal serums. Both low and high mucoprotein levels among the cord blood samples are paired with high, intermediate and relatively low values in the maternal series.

Table 1 includes data showing that the mucoprotein concentration of maternal serum rises sharply in the immediate postpartum period. Distinctly high levels of mucoprotein characterize maternal serum drawn 5 to 30 days after parturition. Following delivery the mucoprotein concentration in the serum of infants increases until a constant level similar to normal adult levels is attained at approximately one month of age. In table 3 muco-

TABLE 4

HYALURONIDASE INHIBITOR LEVELS IN MATERNAL AND INFANT SERUM

Group	No. of Cases	Mean Hyaluronidase Inhibitor-% Inhibition	Range % Inhib.	Standard Deviation	Standard Error of Mean
Newborn Infants (cord blood)	32	21.0	12.5 to 36.4	7.25	1.28
Maternal Blood within 1 hr. postpartum	32	32.1	18.1 to 59.0	7.64	1.35
Infants 5–11 days of age (jugular)	22	23.9	14.0 to 40.3	7.86	1.68
Maternal Blood 5–11 days postpartum	21	36.6	18.3 to 50.5	8.33	1.81
Infants 12–30 days of age (jugular)	14	16.4	12.5 to 20.0	2.04	0.545
Maternal Blood 12–30 days postpartum	4	26.2	16.9 to 35.5	—	—
Normal Children 1–15 yr.	50	21.5	—	3.32	0.714
Normal Adults 18–48 yr.	25	20.3	—	6.66	1.48

protein concentrations in the serums of children ranging in age from birth to 15 years are arranged according to the chronologic age of the subjects. It is apparent from these data that chemical growth with respect to this constituent occurs only during approximately the first 30 days of life.

In keeping with the findings of Hakanson and Glick,[17] the data presented in table 4 show that the serum level of hyaluronidase inhibitor is elevated in maternal serum at the time of delivery and that a further increase takes place during the immediate postpartum period. These data also demonstrate that the serum level of this constituent returns toward normal within a month after delivery. Newborn infants, on the other hand, instead of having elevated levels as do their mothers, have serum concentrations of hyaluronidase inhibitor that do not differ from the established normal values for children and adults.

The relation of the hyaluronidase inhibitor concentrations of the infants' serums to those of their mothers is presented in tables 4 and 5. It may be seen that the maternal serum has a mean concentration of inhibitor significantly greater than that of the infants and that the inhibition of hyaluronidase by the serum of most individual maternal serum samples exceeds that of the corresponding infant. A slight and inconsistent increase in

TABLE 5

COMPARISON OF HYALURONIDASE INHIBITOR LEVELS IN MATERNAL AND INFANT SERUMS

Maternal Serum*		Infant Serum†		Difference (Maternal-Infant)
Patient	Hyaluronidase Inhibitor-% Inhibition	Patient	Hyaluronidase Inhibitor-% Inhibition	Hyaluronidase Inhibitor-% Inhibition
Mrs. D.	30.0	Baby boy D.	14.0	16.0
" W.	34.6	" " W.	12.5	22.1
" R.F.	36.4	" " F.	15.5	20.9
" A.	45.5	" girl A.	30.0	15.5
" T.M.	34.7	" " M.	36.4	−1.7
" M.	25.8	" " M.	16.9	8.9
" H.	30.0	" boy H.	21.3	6.7
" J.H.	35.1	" " H.	18.3	16.8
" M.A.	18.3	" girl A.	17.0	1.3
" B.	27.6	" boy B.	13.8	13.8
" C.	38.7	" " C.	28.9	9.8
" K.A.	26.8	" " A.	35.9	−9.1
" S.A.	25.3	" " A.	16.7	8.6
" D.C.	21.7	" girl C.	13.8	7.9
" O.	37.5	" boy O.	18.3	19.2
" R.K.	35.9	" girl K.	28.6	7.3
" H.M.	43.8	" " M.	13.8	30.0
" E.R.	34.2	" " R.	21.6	12.6
" C.S.	27.2	" " S.	24.6	2.6
" D.J.	18.1	" boy J.	20.6	−2.5
" H.R.	40.5	" " R.	25.6	14.9
" P.R.	26.5	" girl R.	20.6	5.9
" M.R.	42.5	" boy R.	19.3	23.2
" D.K.	38.7	" " K.	25.8	12.9
" E.W.	23.6	" " W.	23.6	0
" A.A.	32.8	" " A.	24.2	8.6
" M.H.	33.3	" " H.	22.2	11.1
" R.K.	38.7	" girl K.	25.8	12.9
" N.	28.6	" " N.	25.3	3.3
" Z.	59.0	" " Z.	24.2	34.8
Mean	33.0		21.8	11.1
S.E.M.	1.60		1.15	1.75

* Blood drawn from antecubital vein within 1 hr. postpartum.

† Blood obtained from placental stump of umbilical cord after delivery of baby prior to separation of placenta.

hyaluronidase inhibitor occurred among the infants in the immediate neonatal period. This change was followed by a return to normal or slightly subnormal levels in the samples taken 12 to 30 days after birth.

DISCUSSION

The fact that maternal and fetal blood differ from each other and that both differ from blood of nonpregnant adults in protein composition has long been known.[18] Plass and Mathew and others[19–21] have summarized the differences in serum protein concentrations

between these groups which have been detected by salt fractionation technics. Electrophoretic analysis has permitted a more incisive evaluation of the differences between maternal and infant serum, and findings based on the use of this technic have been published from several laboratories.[10-12] The data based on use of electrophoretic methods are in essential agreement. Maternal serum at parturition has a relatively low concentration of both albumin and gamma globulin and a relatively high concentration of alpha and beta globulins. Fetal serum obtained from cord blood differs in having relatively high concentration of albumin and low concentrations of alpha and beta globulins. With respect to gamma globulins the fetal serum is even more unique. Not only does the relative concentration of this constituent regularly exceed that in the maternal serum, but fetal serum generally has a higher absolute concentration of gamma globulin than does adult serum in spite of the fact that the total serum proteins of the infant are uniformly low.

In addition, from studies employing electrophoretic methods, Longsworth et al.[10] showed that the concentration of fibrinogen is increased in maternal serum late in pregnancy and that fibrinogen levels of the newborn infant do not differ from those of other age groups. The findings with respect to this well known acute phase reactant are entirely parallel to the findings reported here with respect to hyaluronidase inhibitor.

The data presented in this paper indicate that maternal serum at the time of parturition differs significantly from fetal serum with respect to both of the constituents investigated. The concentration of mucoprotein and hyaluronidase inhibitor in maternal serum are significantly elevated over values found in serum of normal adults of the same age. Fetal serums, on the other hand, differ from maternal serums in that their mucoprotein concentrations are significantly lower than those of normal adults and markedly lower than those of the corresponding maternal serums. The hyaluronidase inhibitor concentrations of newborn infant serum, though not depressed, differ from the concentrations in maternal serum in that elevated levels are uniformly absent in the serums of the infants and regularly present in those of the mothers.

These findings suggest that a placental barrier exists preventing free interchange of nonspecific hyaluronidase inhibitor and mucoproteins between maternal and infant serum. It would likewise seem that the stimuli bringing about elevation of the levels of these acute phase reactants in the maternal serum either do not reach the organ or cell system responsible for their production in the infant, or even though reaching it, find it unresponsive in the immature state. Although little is known of the fundamental aspects of mucoprotein metabolism, evidence has recently been presented[22] indicating that this group of proteins like albumin and alpha globulins are probably produced in the liver. If this is true, it seems reasonable to speculate that in this respect as in many other capacities the liver of the newborn infant is functionally deficient. Particularly significant in clarifying this point would be an investigation to determine whether newborn infants with infection or other acute diseases are capable of developing increased concentration of mucoprotein in their serums.

The finding of elevations of hyaluronidase inhibitor levels in the serum of patients during the course of diverse diseases not obviously related to one another prompted an experimental investigation, the results of which suggest that the adrenal gland plays a role in regulating the concentration of this inhibitor in the serum.[23] The findings here reported of high levels of hyaluronidase inhibitor appearing during the late stages of gestation are in keeping with these experimental findings since adrenal hyperactivity probably occurs during pregnancy.[24] Although these data suggest the existence of a placental barrier with respect to hyaluronidase inhibitor, critical evidence on the nature of this barrier is lacking.

Summary and Conclusions

Normal maternal serum and newborn infant serum have been compared with respect to their content of nonspecific hyaluronidase inhibitor and mucoprotein. Elevations in serum levels of hyaluronidase inhibitor and mucoprotein were found in maternal serum while decreased concentrations of mucoprotein and normal levels of hyaluronidase inhibitor characterized the serum of infants at birth. Mucoprotein concentrations in maternal serum increase for a period following delivery and remain at high levels for at least one month. Increase from low mucoprotein levels occurred in infants' serums during the first month of life and levels comparable to those of normal adults were found throughout the remainder of the first year. The relation of these findings to studies of other protein constituents in maternal and infant serum is discussed as are possible mechanisms to explain the results obtained.

References

1. Good, R. A., in Thomas, L., Rheumatic Fever, Minneapolis, University of Minnesota Press, 1952, p. 115.
2. Kelley, V. C., Acute phase reactants. I. Serum non-glucosamine-polysaccharides in patients with rheumatic fever and related conditions, J. Pediat. **40**:405, 1952; II. Serum hexosamines in patients with rheumatic fever and related diseases, ibid., **40**:413, 1952.
3. Glick, D., Hyaluronidase inhibitor of human blood serum in health and disease, J. Mt. Sinai Hosp. **17**:207, 1950.
4. Dorfman, A., Ott, M. L., and Whitney, R., Hyaluronidase inhibitor of human blood, J. Biol. Chem. **174**:621, 1948.
5. Winzler, R. J., Devor, A. W., Mehl, J. W., and Smythe, I. M., Studies on mucoproteins of human plasma. I. Determination and isolation, J. Clin. Investigation **27**:609, 1948.
6. Kelley, V. C., Good, R. A., and McQuarrie, I., Serum mucoproteins in children in health and disease with special reference to rheumatic fever, PEDIATRICS **5**:824, 1950.
7. Good, R. A., and Glick, D., Mucolytic enzyme systems. IX. Non-specific hyaluronidase inhibitor in rheumatic fever, J. Infect. Dis. **86**:38, 1950.
8. Anderson, H. C., and McCarty, M., Determination of C-reactive protein in blood as measure of activity of disease process in acute rheumatic fever, Am. J. Med. **8**:445, 1950.
9. Rosenberg, C., and Schloss, B., Plasma hexosamine levels in acute rheumatic fever, Am. Heart J. **38**:872, 1949.
10. Longsworth, L. G., Curtis, R. M., and Pembroke, R. H., Jr., Electrophoretic analysis of maternal and fetal plasmas and sera, J. Clin. Investigation **24**:46, 1945.
11. Moore, D. H., DuPan, R. M., and Buxton, C. L., Electrophoretic study of maternal, fetal, and infant sera, Am. J. Obst. & Gynec. **57**:312, 1949.
12. Beach, E. F., and others, Plasma proteins in venous and cord blood at delivery following uncomplicated and complicated pregnancies, Proc. Soc. Exper. Biol. & Med. **80**:234, 1952.
13. Sutliff, W. D., and Finland, M., Antipneumococcic immunity reactions in individuals of different ages, J. Exper. Med. **55**:837, 1932.
14. Fothergill, L. D., and Wright, J., Influenzal meningitis, J. Immunol. **24**:273, 1933.
15. Glick, D., and Gollan, F., Inhibition of hyaluronidase by serum in poliomyelitis, J. Infect. Dis. **83**:200, 1948.
16. Wattenberg, L. W., and Glick, D., Mucolytic enzyme systems. VII. Effects of tissue extracts and body fluids, certain steroids and hemoglobin derivatives on hyaluronidase activity, J. Biol. Chem. **179**:1213, 1949.
17. Hakanson, E. Y., and Glick, D., Mucolytic enzyme systems. VIII. Inhibition of hyaluronidase by human blood serum during normal menstrual cycle and pregnancy, J. Clin. Investigation **28**: 713, 1949.
18. Smith, C. A., Physiology of Newborn Infant, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1951.
19. Plass, E. D., and Mathew, C. W., Placental transmission. IV. Protein fractions in fetal and maternal plasma, Am. J. Obst. & Gynec. **12**:847, 1926.
20. Rapoport, M., Rubin, M. E., and Chaffee, D., Fractionation of serum and plasma proteins by salt precipitation in infants and children. 1. Changes with maturity and age; 2 Changes in glomerulonephritis; 3. Changes in nephrosis, J. Clin. Investigation **22**:487, 1943.

21. Trevorrow, V., Kaser, M., Patterson, J. P., and Hill, R. M., Plasma albumin, globulin, and fibrinogen in healthy individuals from birth to adulthood, J. Lab. & Clin. Med. **27**:471, 1942.
22. Greenspan, E. M., Tepper, B., Terry, L. L., and Schoenbach, E. B., Serum mucoproteins as aid in differentiation of neoplastic from primary parenchymatous liver disease, J. Lab. & Clin. Med. **39**:44, 1952.
23. Good, T. A., Good, R. A., Kelley, V. C., and Glick, D., Mucolytic enzyme systems. XVI. Factors influencing hyaluronidase inhibitor levels in serum, role of adrenal cortex, Am. J. Physiol. **166**:555, 1951.
24. Stander, H. J., Textbook of Obstetrics, ed. 9, New York, D. Appleton-Century Co., 1945, p. 172.

SPANISH ABSTRACT

Enzimas Mucolíticas

XX. Estudio Comparativo en los Sueros Materno y Fetal de las Concentraciones de Mucoproteína y del Inhibidor de la Hialuronidasa

Los cambios en la composición sanguínea durante el período agudo de muchos padecimientos incluyen algunas mucoproteínas ácidas y el inhibidor de la hialuronidasa, que se elevan en las enfermedades agudas y se normalizan al terminar el proceso patológico. En el presente trabajo se hace un estudio comparativo de la concentración de estas substancias en el suero materno y en el del hijo al nacer, de los cambios durante el primer mes después del parto y por último de las concentraciones de mucoproteínas en el suero de niños normales a diferentes edades durante el primer año de vida.

Se encontró que el suero materno difiere del del niño en su concentración mucoproteica y que ambos a su vez difieren en forma significativa del de niños y adultos sanos. La concentración mucoproteica del suero materno durante el parto se eleva y continúa elevándose en el período neo-natal; en cambio, en el suero fetal el nivel de las mucoproteinas es bajo significativamente, con cifras en el niño siempre inferiores a las del suero materno, pero sin ninguna correlación directa entre la concentración fetal y la correspondiente materna. El alza de mucoproteínas en el suero materno se mantiene hasta el mes después del parto; en los niños se observa también ascenso continuo hasta el mes de edad, en que se obtiene un nivel constante similar al de los adultos; el análisis de las concentraciones en niños hasta los 15 años de edad muestra que el ascenso químico de este elemento se presenta sólo durante los primeros 30 días de la vida.

Por lo que respecta al inhibidor de la hialuronidasa se observa una concentración elevada en el suero materno durante el parto y ascenso durante el período post-natal, regresando a sus niveles normales dentro de un mes después. En los niños recién nacidos la concentración del inhibidor de la hialuronidasa es igual a la cifra establecida para niños y adultos. La comparación de la concentración media de este elemento en el suero de la madre y del hijo, muestra valores significativamente mayores en la primera que en el segundo; se presenta un ascenso ligero pero inconsistente en los niños inmediatamente después del nacimiento, alcanzándose el nivel normal de 12 a 30 días después.

Los datos de los autores señalan, pues, que el suero materno difiere en una forma notable del del hijo en el momento del parto, en relación a ambos elementos investigados. La concentración de las mucoproteínas y del inhibidor de la hialuronidasa en el suero materno se encuentra francamente elevada en relación a la de adultos normales de la misma edad; el suero fetal presenta una concentración de mucoproteínas notablemente inferior tanto a la de adultos normales como a la correspondiente materna; el inhibidor de la hialuronidasa se encuentra en el suero del recién nacido a concentraciones no inferiores a las normales de adultos pero sí diferentes de las de la madre pues en el del niño no hay cifras elevadas en ningún caso, mientras que en el suero materno las cifras se encuentran siempre regularmente elevadas.

Estos hallazgos sugieren la presencia de una barrera placentaria que evite el libre intercambio del inhibidor de la hialuronidasa y de mucoproteínas entre los sueros materno y fetal, así como que los estímulos que provocan la elevación de los niveles de estos constituyentes del suero materno ó no llegan al órgano o al sistema celular responsables de su producción en el hijo, o bien que si llegan a ellos no encuentran respuesta. Hay hechos que inclinan a pensar que las mucoproteínas se elaboran probablemente en el hígado; su bajo nivel en los recién nacidos sugiere que, como en otros aspectos, el hígado a esta edad está funcionalmente inmaduro. Como por otra parte se ha visto que las suprarrenales intervienen en la regulación de la concentración en el suero del inhibidor de la hialuronidasa, las altas cifras de este elemento encontradas en las últimas etapas del embarazo sugieren también una hiperactividad suprarrenal durante el mismo.

1940 South Second East

Pediatrics

VOLUME 12 NOVEMBER 1953 NUMBER 5

SPECIAL SECTIONS

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

SECRETARY HOBBY'S VIEWS ON FEDERAL GRANTS-IN-AID

THOSE concerned with the health of children have a rather special interest in the grant-in-aid programs of the Federal Government. Ever since the Sheppard-Towner Act became law in 1921, federal grants-in-aid for maternal and child health have been a prominent part of federal subsidy in the field of health. For the current fiscal year Congress voted an appropriation of $30,000,000 for grants to the States for maternal and child health services, crippled children's services and child welfare services. The Academy, since its origin, has had active interest in and many lively debates over the extent to which the Federal Government should participate in the support of child health services and the training of those rendering the services.

It is therefore appropriate to give particular attention to the view of Mrs. Oveta Culp Hobby, Secretary of Health, Education and Welfare, as stated in an address before the Pasadena Chamber of Commerce. The following is the text of this address:

"There was a time, not so many years ago, when government didn't matter too much to the ordinary citizen or businessman. The functions of government were distinctly limited. It is hard for us to realize that only one generation ago, just before World War I, within the memory of many who are sitting here, all levels of government—National, State, and local combined—spent only half as much as the present interest on the national debt. Many of you can remember the first billion dollar Congress. Today the National Government needs not $1 billion but $60 or $70 billion. And it is not only the Federal Government with its tremendous expenditures for war and defense whose costs have increased. State and local governments, too, have expanded their activities. Today they collect more than ten times as much in taxes as they did forty years ago. California's budget today is as big as the total national budget was forty years ago. Government today collects and spends between one-fourth and one-third of the total na-

tional income. Obviously this affects every man, woman and child in the Nation. As good citizens, as well as businessmen, we should think more and know more about this business of government.

"But in some respects the very growth of government has made it more difficult to keep in touch with it; to keep it in touch with the people. Along with growth has come a shift of responsibility, from local to State, and from State to National Government. Again it is hard to realize that only forty years ago local governments—cities, counties, and school districts—collected and spent about two-thirds of all taxes in this country. The State and National Government shared the remainder. That meant that, in the main, government was close to the people. In local government people know and understand more readily what goes on. They know their officials personally. If they don't like what is done they know whom to hold responsible.

"Today the situation is quite different. The Federal Government now collects about three-fourths of all taxes, and States and local governments share the remainder. Local governments now get less than one-eighth instead of the former two-thirds of the Nation's tax dollar. The expansion of government activities has been at the State and national level. Government has tended to move away from the people.

"Then, too, with the general increase in governmental activity the dividing line between functions of local, and State, and National Government has become blurred. The States and the Federal Government now engage in many activities which were formerly left to local government, or to private interests. We have only to look at the various programs administered by our new Federal Department of Health, Education, and Welfare to see what has happened. Practically all of our expenditures in this Department are for purposes, for functions which are entirely new to the Federal Government within the last twenty years. In many instances these functions are new also to State and local governments. And instead of any given function being carried on by some one level of government, all three levels—local, State, and National—are frequently concerned with the same functions.

"Federal participation in all these fields is largely financial, in the form of grants-in-aid to the States. The actual administration is in the hands of State and local authorities. In public assistance, for example—which is by far the largest and the most expensive of our many grant programs—99.6% of the money appropriated by Congress is passed on to the States, and States frequently pass it on to the localities. But in making the grants the Federal Congress imposes certain conditions. It requires certain standards to be observed in the use of the money. This means that the national agency must interest itself, to some extent, in State and local administration. That gives rise to the charge of Federal interference or Federal dictation which we hear so frequently in connection with the grant programs. This is the crux of the problem of Federal-State relations.

"To me this appears to be one of the most crucial problems of our governmental system today. You will note that I suggested as my topic, 'The Federal-State Partnership.' That was a quite deliberate choice. I think too often we regard the Federal Government and the States as rivals, each trying to extend its jurisdiction and each trying to get a larger share of the citizen's limited tax dollars. That is not a sound conception of intergovernmental relations in a federal system. It may be that some of our difficulties in this field derive in part from such a philosophy. I prefer to think of the States and the Federal Government as partners, each doing its share in the over-all business of government. I am sure government can serve the people better if we take that point of view.

"I'm glad to see this question of Federal-State relations, of grants-in-aid, getting so much public attention. I understand your national organization recently sponsored a conference on the subject. The Governors' Conference at Seattle devoted a half-day to it. And Congress, at the President's request, has established a Commission on Intergovernmental Relations to study the whole subject and make recommendations for action. With this study pending I shall certainly not attempt, today, to produce all the answers. I don't know the answers. But I do know many of the problems, and I should like to think with you about how this idea of a Federal-State partnership can be applied to some of these problems.

"For purposes of discussion I shall talk in terms of programs within my own Department. There are other grant programs, of course, and I suppose there are problems of Federal-State relations in these programs, too. But the bulk of Federal grants are in the fields of health and welfare, and the principles with which I shall deal are applicable, I am sure, to grants-in-aid anywhere.

"In the first place I think we must recognize that whatever is done about grants-in-aid, the activities now supported in part by grants will continue. While they may have been stimulated, in the first instance, by grants, they have become so much an established part of State and local government services that they are not likely to be much decreased. In our discussion, therefore, we are not concerned with whether or not a given function should be dropped or continued, but rather with who shall perform certain functions, and how they shall be financed.

"There are two different ways in which we may approach this question. We may try to separate the functions, allocating some to the Federal Government and some to the States—and perhaps some others to the local communities. Each jurisdiction would presumably be fully responsible for the function in question. This allocation of functions is the usual suggestion. It has much to recommend it. It is simple; responsibility and authority are clear and undivided. There can be no overlapping, or duplication, or conflict. To the extent that programs can be adequately maintained in this way, without undue burden in some parts of the country, it seems to me this would be a desirable solution for at least some of the problems.

"Even so, it is not always easy to determine which functions should be performed by the States and which by the National Government. Both are interested in the welfare of the people. But ours is a Federal system and the Federal Government is now so burdened with international and strictly national matters that wherever possible what might be called the domestic functions should, I believe, be left to the States. Of course there is always the temptation to assume that the larger jurisdiction is necessarily wiser or stronger, and can perform a given function better than the smaller jurisdiction. This is a temptation we must resist. The strength of our Nation lies not in building up a huge central government but in maintaining strong and vital State governments. As President Eisenhower said to the Governors at Seattle earlier this month, unless we find ways to strengthen and vitalize State Governments, our system of government as we have known it will cease to exist. I believe, therefore, that insofar as possible most of these activities with which we are concerned should be decentralized to the States.

"Here we run into some serious difficulties. These activities are expensive. In many States welfare costs are second only to the cost of education in State budgets. For the country as a whole, the Federal Government, through grants, bears a little over half of this cost. If these grants were to be discontinued and the States attempted to carry on

their programs, the increased burden on State treasuries would be enormous. And unfortunately the largest relative burden would fall on the States with low incomes. These are the States where the Federal Government now contributes 60-70%, or even more, of the cost of some of these programs. And, in the main, these States are already taxing their resources very heavily, in some instances 20-25% more than the national average. It is difficult to see where they would find the revenues to carry on these services even at a minimum level.

"To help meet this situation it is generally proposed that certain taxes now collected by the Federal Government be discontinued so that the States can use these sources of revenue. I might point out, in passing, that such an exchange of taxes for grants would not relieve the Federal budget in any way. Also, it is by no means as simple and complete a solution of the problem as it appears on the surface. If the Federal Government discontinues a given tax it must apply that policy nationwide. It cannot collect a given tax in one State and not in another. Unfortunately there is no assurance that any tax or group of taxes which might be selected to be turned over to the States will provide revenues, in individual States, which will be in any way related to the need for funds to replace the grants which are to be discontinued.

"Let me illustrate what I mean. It is commonly suggested that the taxes on amusement, and on local telephone service, and the gift and death taxes would be suitable for State rather than Federal collection. This seems reasonable. These particular taxes would be as evenly distributed among the States as any that could be found. The total yield of those three taxes is about equal to the total grants made by our Department. But the distribution among the States of the grants now being made, and of the potential tax yields, would be quite different. In general, the taxes would provide revenue largely in the States with high per capita incomes, while grants go somewhat more to States with low incomes. The 29 States with incomes below the national average get about 52% of the grants made by our Department, but they would get only 25% of these taxes. In individual States the difference is even more striking. Several States with the highest per capita incomes would derive three, and even four times as much from these taxes as they now get in grants; while some States with much lower incomes would collect in taxes only one-fourth as much as they are getting in grants.

"This points up the basic problem which must be faced. The needs which are to be met—aid to the aged, blind, the disabled, and assistance to mothers and dependent children, etc.—are greatest in the States where incomes are relatively low. In these States, resources to meet the needs are limited. In States where incomes are high and resources relatively more adequate, the need to be met is much less. And any attempt to give the States added tax revenues instead of grants will give relatively more aid to those States with large resources, and relatively less to those with small resources.

"In such a situation a complete decentralization of these functions seems impracticable. We have, here, the basic reason for grants-in-aid. The grant is another form of Federal-State partnership. Instead of each partner assuming completely responsibility for certain functions, each contributes to a given function that which he can do best. Unquestionably these programs can be administered best by State and local authorities. That responsibility should be theirs. It is equally clear that many States cannot raise the necessary revenues to finance the programs without unconscionable tax burdens on their limited resources. The grant is a device through which the National Government and the States cooperate; the Federal Government using its over-all taxing authority to provide funds,

and granting these funds to the individual States so they can meet the needs of their people without too heavy a tax burden in individual States.

"I realize that this grant-in-aid procedure is not without its dangers. If there are too many conditions attached, if there is too much detailed supervision by the granting agency, a system of grants may result in expensive and confused administration and in centralized control. It has sometimes worked that way. But this is *not* inevitable. There is no need to throw out the baby with the bath. I am convinced that the necessary conditions can be made simple and clear, so these difficulties need not arise. Supervision and control, too, can then be at a minimum and consist, in the main, of consultation and help to the States in improving their programs. So constructed and so administered a system of grants-in-aid will not weaken State government or centralize control. On the contrary, by enabling States to meet the increasing demands made upon them, such grants will constitute a real source of strength for State governments.

"To summarize then, this business of government has become so huge, and so complex that the Federal Government and the States must share responsibility; they must act as partners in serving the people. In the main, every function should be the responsibility of one level of government, to avoid overlapping and confusion. The Federal Government has such heavy responsibilities in connection with international and purely national matters that the domestic functions should be left to States insofar as possible. But the industrial and financial structure of our country is such that much of the tax-paying ability is located in a limited number of States, while other States lack resources to carry on, alone, some of the essential services. And the Nation as a whole does have a residual responsibility, even for some of these domestic functions, in situations where individual States are unable to provide them. In such circumstances a system of grants-in-aid, properly organized and administered, can assist States in meeting their obligations and prevent the transfer of these functions to the central government.

"I have not attempted, today, to suggest ways of dealing with any particular function or problem. Neither do I have time to discuss the complex question of old-age and survivors insurance and its relation to public assistance. If the insurance program is extended as President Eisenhower has recommended, it will, in time, reduce considerably the need for public assistance. But there are a number of other grants and the nature of the problems involved are the same. I have tried to view these problems as a whole, and see in what direction we may look for solutions.

"All of these matters I have mentioned will be before the Commission on Intergovernmental Relations. We hope to benefit greatly by its work. I was glad to hear that the Chamber of Commerce is planning to cooperate with the Commission. In your deliberations I trust that you will give some thought to the things I have mentioned today. I should like to see much more such citizen interest in these matters. In these days of big government—and in spite of every economy it will still be big—our first effort must be to keep government as close as possible to the people, and to promote interest in and understanding of the business of government. When the help of the Federal Government is essential, we should make sure that the Federal Government and the States operate as an effective partnership, based on mutual respect and confidence. Only so can we be sure to preserve our Federal system."

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

INCREASINGLY, in recent years, pediatricians have been called on to work with the problem of juvenile delinquency. Published statistics on crimes and antisocial activities by children have sometimes been frightening, and loose remarks are often made about drastic remedies being needed to "curb" modern youth. In such a situation, parents naturally turn to their physicians for advice and counsel.

Within the community pattern of the attack on juvenile delinquency, the "juvenile court" has a central role. If the ignorance of this editor is any index, pediatricians, in general, know little of the structure, responsibilities, jurisdiction, community relationships, and standards of juvenile courts. It is, for example, both revealing and reassuring to learn that ". . . the court stands in the position of a 'protecting parent' rather than a prosecutor. . . ."

The National Probation and Parole Association, a nonprofit citizen and professional organization with professional and technical staff, seeks to extend and improve probation and parole services for both children and adults throughout the country, to promote juvenile and domestic relations courts and to develop specialized facilities and programs for the detention of children. At the request of the editor, Mr. Will C. Turnbladh, Executive Director of the Association, has prepared the following interesting and informative article on the background and some of the problems of juvenile courts.

JUVENILE COURTS IN THE U.S.A.

By WILL C. TURNBLADH*

THE juvenile court is itself a "child" within the centuries-old judicial system, but it is a child that has learned to walk and talk for itself at an early age. In the United States, the first efforts to obtain special treatment for children within the judicial and penal systems came during the Nineteenth Century; in 1824 New York established a juvenile institution to prevent imprisonment of children with adults, and in 1869 Massachusetts passed a law requiring a "state visiting agent" to "attend all hearings whenever application is made for the commitment of a child to a reformatory." In some courts it became customary to provide special hearings for children. Then, in 1899, this trend culminated in the establishment, in Chicago, of the first separate juvenile court.

At first, the idea behind the separate juvenile court was a negative one, based on the feeling that children should not be treated as adult criminals. From this negative beginning, however, a very positive philosophy has developed—a philosophy quite different from that of adult criminal courts. Its legal basis is founded on two principles: first, that a child cannot be held responsible for criminal acts until a much later age than the common law limit of seven years; and, second, that although brought within the jurisdiction of

* Executive Director, National Probation and Parole Association, New York City.

the court, the child is not accused of a crime nor regarded as a criminal. Instead, the court stands in the positon of a "protecting parent" rather than a prosecutor, and it is assumed that not only the neglected child, but also the child whose behavior is dissocial, stands in need of care. The juvenile court, in short, is intended to provide the care, custody, or discipline which the child needs and which should have been given by the parent. And, in many modern juvenile courts, this concept of care of the child has been broadened to include treatment of the child through medical, psychiatric, social casework, and other technics in order to undo, insofar as is possible, the unfortunate results in the child of the lack of care he has received in the past.

Within 10 years after the establishment of the first juvenile court in Chicago, the movement had extended to 22 states, and now juvenile courts in one form or another are a part of every state judicial system. Also, all of the large cities have special courts for children.

As would be expected in a country as individualistic as ours, the organization of juvenile courts varies widely from state to state, and even within a given state. It would be impossible, in so short a space, to describe in detail all the different systems under which juvenile courts operate. But a few examples may serve to show some of the major differences and to point up the need for constructive reorganization of this important segment of our judicial system.

While there are many minor variations, the organization of juvenile courts falls into three major types. The commonest of these is to make the juvenile court part of an existing adult court, with the county or district as the geographic unit. Under this plan, the county or district judge holds separate hearings (usually at a specially designated time on his calendar) on juvenile cases, and during such hearings the court is designated as a juvenile court. The obvious defect in this plan is that the judge is elected or appointed primarily as an adult criminal judge, with little regard to his special qualifications for handling juvenile problems. In many courts having several judges, this situation is further aggravated by the use of a rotation system, whereby each judge serves as juvenile judge for only a few weeks or months, then turns this highly specialized task, and a specialized task it is, over to the next judge in rotation.

A second plan, found unfortunately in only a few states, is to establish completely separate juvenile courts on a statewide basis, each covering a county or group of counties. In states having this system, juvenile court judges are appointed and can be selected with an eye to their special qualifications for this work.

A third plan has separate juvenile courts in some areas, usually urban, while the regular courts perform the juvenile court function in the balance of the state, usually the rural. One problem under this setup is to secure an adequate and uniform juvenile court law, or, if such a law has been passed, to secure uniform application of the law in the various courts.

In the matter of jurisdiction, too, there is great variation from state to state. In most states, the juvenile court has exclusive jurisdiction of all matters involving the delinquency, neglect, or dependency of children under a specified age(which varies from 15 to 21) with certain very specific exceptions. In one southern state, for example, the juvenile court has such exclusive jurisdiction over all children under 17; except that children who are 15 or over, and who have committed a capital offense (first degree murder or aggravated rape) may be tried in criminal court. In other states, children above a given age, but still within the statutory definition of a juvenile, may be referred to the criminal court by the

juvenile court for certain of the more serious offenses. In still other states, the reverse is true; that is, the criminal court, although having original jurisdiction, may refer persons under a specified age to the juvenile court, if it is felt to be the best interest of the individual and of the community.

Many state juvenile court laws do not specify a minimum age limit for delinquency, but in practice the common law limit of seven years is generally accepted. On the other hand, all state statutes set a maximum age limit. The trend, in recent years, has been to raise this maximum age limit, and it now stands at "under 18" in most states. In those states where the age limit is higher than 18, the juvenile court usually has concurrent jurisdiction with the criminal court over all juveniles over 18.

An important fact to keep in mind is that the jurisdiction of the juvenile court is established by law; it is not left to the discretion of a policeman, deputy sheriff, or other individual to determine whether a particular child shall be taken to the juvenile court or to some other court. Thus if a youngster, through some error, is charged in a criminal court, the judge of that court is required by law to declare himself without jurisdiction and to transfer the case to the juvenile court.

The development of a new philosophy in juvenile court has resulted, among other things, in an entirely different concept of "trial." In fact the term "trial" is not even used in the vast majority of juvenile court statutes, the word "hearing" being substituted as more compatible with the concept of protection instead of punishment. Most state laws require that juvenile court hearings be held in chambers, or other suitable private place, rather than in open court, and that the general public be excluded from such hearings. They also specify that the hearings shall be conducted in an informal manner, often including such phrases as "in such a manner as to gain the confidence of the child and to allay his fears."

Usually the subject of trial by jury is not mentioned in juvenile court laws, though a few specify that no jury shall be used. A few others provide for jury trial on demand or in specific situations. However, several state supreme court decisions have held that the constitutional right to jury trial does not apply in delinquency cases.

In general, juvenile court laws allow the judge wide latitude in his choice of dispositions, indicating that the disposition should be geared to the needs of the particular child rather than based upon the nature of the offense. Thus the laws themselves uphold and foster the philosophy of the juvenile court that the child or youth appearing before the court is not a criminal, nor guilty of any crime, but is a child in need of the protection and the care of society.

The juvenile court has emerged as a new strong entity in our American life. It is no longer a criminal court in short pants. The laws of most states give it ample jurisdiction and power to protect children and to protect the community. The critical problem in so many communities is to provide the juvenile court with the services essential to the effective discharge of its great responsibilities to youth. What are some of these services?

A specialized home-like detention facility for the relatively few youngsters who are so disturbed as to require secure custody for their own protection or that of the community for a short period while the court determines the nature of their problems and the type of care and treatment needed. The rehabilitation process for the child can begin in a well staffed detention home; it is immeasurably set back if not defeated when the youngster is held in the jail or jail-like detention "home."

Psychiatric and psychologic services readily available for study and treatment. The

juvenile court confronted as it is with some of the most complicated problems of children and families in the community is entitled to the best obtainable clinical help.

Intermediate facilities providing group therapy, vocational training, and hostel type residence for older youths who do not have or cannot remain in their own homes. These teen agers require a definite program of guidance and supervision during the painful process of maturing. For lack of intermediate facilities, far too often the only possibility open to the juvenile court is commitment to the state correctional school.

Professionally qualified probation officers in sufficient numbers to assure individualized study of each case and individualized guidance and supervision of youngsters in need of this help at a crucial time in their lives.

A judge with the insight, understanding, patience and temperament to deal intelligently with the problems of children and families day in and day out. A judge whose assignment permits him the time and opportunity to concentrate and specialize on one of the most important posts in our entire judicial system.

In our efforts to cope with the problem of youth delinquency we fluctuate between sporadic attempts at prevention and reliance upon jails, training schools, and reformatories. Certainly all those things in a family, neighborhood, and community which promote mental, physical, and spiritual health, prevent delinquency. The well equipped juvenile court itself is a major instrument for prevention of delinquency and crime. The plain fact is that juvenile courts of the nation are, each day, dealing with thousands of youngsters, many in deep conflict with themselves, their families, and society. If we are going to act intelligently and realistically on this national problem we must provide the juvenile courts of all communities with the tools and resources they require. In some states this may demand a state juvenile court system; in some a geographic redirecting or enlargement of the court's jurisdiction to include certain family matters. Subsidies or staff from the state may have to be pumped into less populous areas. With few exceptions the courts or city with a population of over 75,000 should have a sufficient base of tax income and community chest support to provide the facilities and services needed.

The experiences of well organized juvenile courts have clearly demonstrated the dynamic contribution of the juvenile court to the protection of youth and the strengthening of our entire community fabric.